OECD GUIDANCE DOCUMENT FOR THE DERIVATION OF AN ACUTE REFERENCE CONCENTRATION (ARFC)

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Notice

This is a draft of a preliminary document. It has not been formally released by EPA and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.

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Quality Assurance Procedures

Quality assurance procedures have been applied to all information discussed and reported in this document. Applications of these procedures were strategic, focusing on areas most prone to error. For this document, these areas included scientific verisimilitude (e.g., conveying study results in the proper context), transpositional accuracy (e.g., confirmation of transposed quantitative values from their source), and quantitative accuracy (e.g., confirmation on the correct use of models and arithmetic manipulation applied to transposed information).

The specific quality assurance procedures applied in the preparation of this document included review directed especially at these areas by the authors, and by internal EPA scientists as well as through two levels of scientific management clearance to assure that correct data are cited from published papers to exemplify the dose-response assessment approaches of the four acute dose-response assessments (Acute RfCs). Authors and internal reviewers also verified the alignment of outputs from benchmark dose (BMD) and categorical regression (CatReg) software with input data and conclusions regarding point of departure determinations. Dose-response formulas and conversion algorithms were verified by internal reviewers; associated calculation of points of departure and acute RfCs were verified by authors and reviewers. Clearance procedures included questions to authors regarding assurance of data, formula, algorithms, and calculations. In regard to quantitative accuracy, all calculation steps and all data used in those calculations are provided directly within the document to assure transparency and provide access for any user to confirm the calculations.

The intent in applying these quality assurance measures to specific areas having potential for error is to increase the confidence of the overall process and further decrease the uncertainty that is inherent in these processes and procedures.

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1. INTRODUCTION AND OVERVIEW

1.1 Purpose of This Document

1. This document is an initial installment in a stepwise development process for an acute inhalation methodology. It is intended to be a useful and useable guide through the specifics of developing an acute inhalation reference concentration (Acute RfC) offering concrete examples of actual databases, complete with issues, for several chemicals. A methodology developed independent of concrete examples or case studies will likely result in unanticipated situations that severely restrict or prevent the application of the method, and this situation has occurred with methods previously developed. It is to minimize such unanticipated problems that a stepwise approach using real chemical examples is being utilized in the effort to develop an Acute RfC methodology. Supplements to this document will follow to address issues not covered herein.

2. This Preliminary Methodology Document is expected to change over time to incorporate new developments in toxicology and risk assessment and new policy guidance of the Agency. To allow for the timely incorporation of new developments, the methodology should be viewed as a framework for developing Acute RfCs and not as stringent procedural requirements. The vision for the preliminary methodology is that it will be revised and additions made as more illustrative less-than-lifetime assessments are undertaken; this document does not comprise the entirety of this methodology. This iterative process of example assessments guiding methods and vice versa will culminate in a final methodology that is useful over a wide array of situations.

3. The basis for chemical risk assessment within the U.S. Environmental Protection Agency (U.S. EPA) is the publication of the landmark document by the National Research Council, *Science and Judgment in Risk Assessment* (National Research Council, 1994). The NRC document and its 1983 predecessor established the risk assessment paradigm upon which assessments performed within the agency and beyond have been based. That paradigm consists of four steps: (1) Hazard Identification, where the toxic potential for an agent is determined; (2) Dose-Response Assessment, where the quantitative relationship between the dose and the toxic response is determined; (3) Exposure Assessment, where the potential routes of exposure and the magnitude, duration and timing of exposures are determined; and (4) Risk Characterization, where the integration from the previous three steps is performed to formulate a recommendation that can be used by the risk manager in determining acceptable risk. This paradigm is applied in deriving the Acute RfC, which represents the dose-response step.

4. One purpose of this Preliminary Methodology Document is to provide a description and to update the reader in general terms on the methodology for deriving Acute RfC values that is currently under development by the National Center for Environmental Assessment (NCEA) of the U.S. EPA. Essentially, an Acute RfC is the quantitative exposure-response assessment for noncancer effects after acute exposure to inhaled chemicals other than criteria air pollutants. For the purpose of this document, acute exposure is defined as a continuous or near-continuous exposure for 24 h or less, which is in keeping with the U.S. EPA Risk Assessment Forum (RAF) guidance (U.S. EPA, 2002). Acute exposure to toxic air pollutants can occur as a result of accidental releases as well as routine releases. The Acute RfC is intended to be used as a tool in health risk assessment for both of these exposure scenarios, subject to limitations also discussed in this Preliminary Methodology Document.

5. The primary purpose of this document, however, is to orient the assessor to the challenges associated with deriving reference values for acute inhalation exposures to chemical agents in general and to provide a guide in managing those challenges. This guidance is provided preliminary to the publication of the completed final method.

6. Included in this introductory chapter are summary comparisons to a number of existing acute reference value systems. The methods used in deriving many of those acute reference values have been applied in developing the four example acute assessments discussed in this document (ethylene oxide

[EtO], hexachlorocyclopentadiene [HCCPD], hydrogen sulfide [H_2S], and phosgene) and have helped inform the developing acute inhalation assessment method.

7. "Acute" in the context of this discussion refers to the length of exposure and not necessarily the type of effect. Acute exposure to a chemical may result in chronic health effects as well as immediate, acute effects. The RAF defines acute exposures as "a continuous or near-continuous exposure for 24-h or less" (U.S. EPA, 2002); however, considerable variability exists in how different organizations define the length of time comprising an acute exposure, as will be discussed more fully.

8. The focus of the reference values discussed herein, and for the Acute RfC, is on health effects, although there can often be an overlap with other potential adverse properties of the individual chemicals, such as flammability or explosive potential. Acute RfCs are intended to have the same status as the Chronic RfC values on the Integrated Risk Information System (IRIS).

1.1.1 Comparison of Reference Values

9. Occupationally based reference values for acute exposures were initially developed in the first half of the twentieth century, much earlier than other types of acute reference values. Community-based acute reference values are more recent developments, and much of the impetus to develop those acute effect levels can be traced to the incident in Bhopal, India, in 1984. In the years following that event, the Right-To-Know (RTK) provisions of the Superfund program were enacted under the Superfund Amendments and Reauthorization Act, SARA, (1986). Section 112(r) of Clean Air Act Amendments of 1990 (CAAA) established a list of chemicals that were considered hazardous and posed a potential risk for catastrophic accidental release or that had the potential to create a risk of explosion. Facilities that maintain or handle significant quantities of listed chemicals are required to develop risk management plans, including defining areas for evacuation in case of an emergency such as a catastrophic release. These plans are shared with local first responders (police and fire departments) and U.S. EPA Regional offices. Additional initiatives for such releases were also instituted by a number of State governments.

10. Reference values for health protection of the general public that are not based on emergency response are even more recent. The 1990 CAAA provisions for regulation of Hazardous Air Pollutants (HAPs) stipulate that U.S. EPA consider risks from HAP-emitting facilities for both chronic (long-term average) and acute (short-term excursions from the average) exposure scenarios (Section 112(b)(2), revision of the list; and Section 112(f), residual risk). The short-term excursions may occur more routinely than the catastrophic accidental releases under Section 112(r) of the CAAA, and the reference values for accidental releases may not be appropriate for these "more routine" exposure scenarios.

11. Table 1-1 presents some definitions of terms and comparisons among many of the various reference value systems that are examined more fully here, and in the review by Woodall (2005).

Occupational Reference Values

12. Occupational reference values usually assume a "healthy worker" population (e.g., 20- to 65-year-old workers healthy enough to work a full day), with any susceptible individuals self-selected out of that line of work (i.e., if the work conditions are unbearable for a susceptible person, they usually find other work). The exposure scenario assumes an average workday and workweek (8- to 10-h per day and 40-h per week, respectively) with the potential for some short-term peaks occurring during those averaging periods. The basis for occupational reference value derivation can also vary by chemical. Some reference values weigh the technical feasibility and/or monitoring cost for acceptable exposure levels against potential adverse health effects. For certain chemicals, reference values may be based on the lowest concentration that can be measured accurately, although lower exposure levels may be preferable, based on health-effects considerations. Examples of occupational reference values include the Recommended Exposure Limits (RELs) and Short-term Exposure Limits (STELs) developed by the National Institute for Occupational Safety and Health (NIOSH); the Permissible Exposure Limits (PEL), which is usually based on an 8-h time-weighted average (PEL-TWA); and ceiling values for 15-min exposure periods [PEL-TWA and Ceiling values were both developed as enforceable workplace limits by the Occupation Safety and

Table 1-1. Acute Reference Value Definitions (adapted from Woodall, 2005)

Reference Value	Organization	Type Value	Exposure Duration
PEL - Permissible Exposure Limit	OSHA	Occupational	8-h (TWA)
Ceiling	OSHA	Occupational	Up to10-min
REL - Recommended Exposure Limit	NIOSH	Occupational	8-h (TWA)
IDLH - Immediately Dangerous to Life and Health	NIOSH	Occupational	Up to 30-min
STEL - Short-Term Exposure Limit	NIOSH	Occupational	15-min (TWA)
TLV - Threshold Limit Value	ACGIH	Occupational	8-h (TWA)
TLV-STEL - TLV Short-Term Exposure Limit	ACGIH	Occupational	15-min (TWA)
AEGL - Acute Exposure Guideline Level	NAC/AEGL; COT/AEGL	Emergency Response	10- and 30-min; 1-, 4- and 8-h
ERPG – Emergency Response Planning Guideline	AIHA	Emergency Response	1-h
TEEL – Temporary Emergency Exposure Level	DOE	Emergency Response	1-h
ERG – Emergency Response Guidebook	DOT	Emergency Response	Specialized application to determine evacuation zones
MRL - Minimal Risk Level	ATSDR	Public Health	1-14 days (acute); 15-364 days (intermediate); >365 days (chronic)
REL - Reference Exposure Level	OEHHA	Public Health	1-8 h
Acute RfC - Acute Reference Concentration	U.S. EPA	Public Health	1-, 4-, 8-, and 24-h

ACGIH = American Conference of Governmental Industrial Hygienists
AIHA = American Industrial Hygiene Association
ATSDR = Agency for Toxic Substances and Disease Registry
COT = Committee on Toxicology of the National Academy of Sciences
DOE = Department of Energy
U.S. EPA = U.S. Environmental Protection Agency
DOT = Department of Transportation
NAC = National Advisory Committee
NAS = National Academy of Sciences

Health Administration (OSHA)]; and the Threshold Limit Values (TLVs) developed by the American Conference of Governmental Industrial Hygienists (ACGIH). Other similar types of values have been generated in other countries (e.g., the MAC in the Netherlands and MAK in Germany that both emulate the TLV-TWA values).

Emergency Response Reference Values

13. Emergency response reference values are designed for the general population but not necessarily for the "most susceptible" subgroups within that population. They are designed for rare, short-term exposures (so-called once-in-a-lifetime events) and do not have the same "margin of safety," and are therefore usually at higher levels than the more protective public health reference values (described below). The reason for this relatively higher health-effect threshold is to avoid the possibility for creating panic, and the ensuing risk to life and safety, that may be caused by evacuation in a potentially affected area and of having incidents occur too frequently for these supposedly "rare" events. Some other differences between the emergency response and public health reference values are discussed more fully in later sections of this document. Examples of emergency response reference values in Table 1-1 include the Acute Exposure Guideline Levels (AEGLs), Emergency Response Planning Guidelines (ERPGs), and Temporary Emergency Exposure Levels (TEELs). Particularly useful to first responders in determining evacuation zones are the Emergency Response Guidebook (ERG) values, which are developed by the U.S. Department of Transportation (U.S. DOT) (2004), and updated every four years.

General Public Protective Reference Values

14. Public health protective reference values are generally more health protective than either occupational or emergency response values and attempt to include most susceptible individuals, but not always the hypersusceptible. They are designed for more routine, potentially repeated exposures, in contrast to the emergency response reference values that are designed for rare, "once-in-a-lifetime" types of events. Examples of these types of values include the acute RELs, developed by the California EPA Office of Environmental Health and Hazard Assessment (OEHHA) (not to be confused with the National Institutes for Occupational Safety and Health [NIOSH] RELs [see above]), and the Acute RfC described in this document.

1.1.2 Regulatory Need for Acute Inhalation Reference Values

15. A methodology for health assessment of acute inhalation exposures is essential for risk assessment of both routine and accidental releases. Although these methods are intended for broad application to inhaled chemicals, they were specifically developed in support of the Clean Air Act as amended in 1990 (CAAA) (U.S. Congress, 1990). CAAA Section 112(b)(2) describes hazardous air pollutants as being among other things, "acutely or chronically toxic." The major needs for the methodology are listed below:

16. Development of emission standards based on the maximum achievable control technology (MACT) for major sources of 188 listed pollutants (Section 112(d) of the CAAA). A further requirement of the CAAA is the evaluation of residual risk from listed source categories after application of MACT, and further regulation, if needed, to provide an "ample margin of safety to protect public health." Implementation of the CAAA requires methods for assessment of risk for noncancer endpoints from acute and chronic exposures caused by routine or accidental releases of toxic chemicals to the atmosphere.

17. Consideration of hazard and/or risk are the basis for decisions regarding additions or deletions from the hazardous air pollutant list (Section 112(b)(3)(A)), delisting from the source category list (Section 112(c)), and additions to the accidental release list (Section 112(r)).

18. Risk analysis of potential accidental releases to identify potentially affected populations for risk management planning in the case of accidental releases that might cause serious health effects [Section 112(r)].

19. The original CAA (U.S. Congress, 1973) also requires the development of primary National Ambient Air Quality Standards (NAAQS) which are health-based exposure standards intended to protect sensitive subpopulations from adverse effects of exposures to the criteria air pollutants with an ample margin of safety. Because the process for developing NAAQS is explicitly governed by the CAA and involves considerable scientific and public review, the method for deriving Acute RfCs will not necessarily be applied to the criteria air pollutants (ozone, nitrogen dioxide, sulfur dioxide, particulate matter, lead, and

carbon monoxide). NAAQS are standards with legal obligations for attainment, whereas Acute RfCs are toxicity reference values or benchmarks to be used for acute inhalation risk assessment.

20. Although developed specifically to support the requirements for noncancer risk assessment called for in the CAAA of 1990, Acute RfCs are amenable to broader applications. Acute RfCs can be used as toxicity benchmarks for risk assessment for acute inhalation exposures to any inhaled chemical.

21. The U.S. EPA, through the Superfund Program, has been given responsibility by Congress under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) to perform time-critical removal actions [42 USC 9604(a)1(B)] that often require acute and other less-than-lifetime reference values to determine the appropriate action. Additionally, CERCLA obligates the Agency for Toxic Substances and Disease Registry (ATSDR) to develop Toxicological Profiles for the most common substances found at National Priority List (NPL) sites; however, Toxicological Profiles have not been developed for all substances encountered and for those substances with Toxicological Profiles, not all have developed acute values. ATSDR and the Integrated Risk Information System (IRIS) program within the U.S. EPA currently have a memorandum of understanding (MOU) that promotes maximal cooperation and minimal duplication in developing reference values. Development of an acute inhalation health risk assessment guidance and methodology will be useful in both programs.

22. More recently, the National Homeland Security Research Center (NHSRC) within the U.S. EPA has been developing acute, short-term, and long-term reference values in response to Homeland Security Presidential Directive Number 8, "National Preparedness," dated December 17, 2003. HSPD No. 8 specifically requires Federal agencies to develop national emergency preparedness guidelines for domestic terrorist incidents or natural disasters. Thus, Provisional Advisory Levels (PALs) are being developed as threshold limits of acute, short-, and long-term duration exposures for the general public. These exposure values are appropriate for establishing health-based criteria for evacuation and re-entry into buildings, use/reuse of drinking water, and cleanup of contaminated facilities. There has been active coordination between NCEA, NHSRC, and the AEGL programs in the effort to develop PALs in the NHSRC program, and consideration of these types of values has also been incorporated into the developing less-than-lifetime inhalation risk assessment methods.

1.1.3 Development of this Document

23. Work on acute inhalation exposures at NCEA began in the early 1990s with the development of an internal database of chemical-specific acute toxicity information (Guth and Raymond, 1996). The database was developed by extracting experimental protocol and results information from acute toxicity studies so that the information could be readily available for use in testing approaches to developing acute toxicity benchmarks. The first draft Acute Reference Exposure (ARE) document was written in 1994 and peer-reviewed by external reviewers in a workshop format. The draft ARE document was subsequently revised and then reviewed by U.S. EPA's Science Advisory Board (SAB), and later by the U.S. EPA Risk Assessment Forum (RAF).

24. This Preliminary Methodology Document draws heavily from the draft ARE method document (U.S. EPA, 2000a), and the SAB and RAF comments on that document. This Preliminary Methodology Document also draws upon the comments that have come from the RAF on improving the reference dose/reference concentration (RfD/RfC) development process (U.S. EPA, 2002), and from Staff participation in the IRIS Program's pilot project to implement RAF suggestions. NCEA Staff have also participated as the Office of Research and Development representative on the National Advisory Committee for Acute Exposure Guideline Levels (NAC/AEGL) and as advisor in the NHSRC PAL program. These experiences have also contributed to this document's development.

25. The development of noncancer risk assessment has been characterized by reliance on standard methods with default options that have been incrementally updated to implement recent advances in the science of toxicology. In the area of noncancer risk assessment, examples of incremental addition of more sophisticated and relevant methods to the default approaches include the incorporation of dosimetry, pharmacokinetics, quantitative exposure-response analysis, and mechanistically based dose-response models. The addition of the interspecies dosimetric adjustments based on kinetic modeling to the derivation of inhalation RfCs for chronic noncancer effects is an example of the addition of new techniques

to an established U.S. EPA method. The incorporation of quantitative dose-response models in the form of curve fitting techniques (i.e., benchmark concentration [BMC] methods) into the derivation of the RfC has lead to a similar improvement of the standard approach, while retaining many of its current features. The methodology described in this document combines these developments with recent advances in categorical regression (CatReg) analysis and other meta-analytical approaches to dose-response assessment.

26. In very general terms, the Acute RfC is derived by identifying a point of departure (POD) and dividing by uncertainty factors (UFs). The most appropriate approach (e.g., No-Observed-Adverse-Effect Level [NOAEL], BMD/C, CatReg) for identifying a POD is determined by the amount and type of available toxicity data. If supported by sufficient data, the preferred approach is to use a mathematical dose-response model to estimate the lower bound on the exposure/concentration predicted to result in a specified response (BMC) or severity (categorical regression). This lower bound is used as the POD for development of the Acute RfC. If the database will not support the use of a dose-response model, the NOAEL and/or Lowest-Observed-Adverse-Effect Level (LOAEL) can be directly identified from the literature and used as the POD. Once the POD is identified from either the lower bound of mathematical models or the experimental NOAEL/LOAEL, it is typically adjusted to a human equivalent concentration (HEC) via dosimetric procedures and then divided by UFs as needed to account for recognized data gaps and resulting uncertainties in the extrapolation from the experimental conditions to the human exposure scenario.

1.2 Acute Reference Concentration: Definition And Application

27. The Acute RfC is an informed estimate of the highest inhalation exposure (concentration and duration) that is unlikely to cause adverse effects in a human population, including sensitive subgroups, exposed to that scenario even on an intermittent basis. Acute exposures are single continuous exposures lasting 24-h or less; Acute RfCs may be derived for any duration of interest within that period, but will typically be developed for 1-, 4-, 8-, and 24-h, depending on the available data. "Intermittent" implies sufficient time between exposures such that one exposure has no effect on the health outcome produced by the next exposure. Thus, intermittent acute exposures are expected to occur relatively infrequently (e.g., no more frequently than monthly for most chemicals). Although not discussed in this document, the method for determining an adequate "recovery period" for a subsequent acute exposure will be the subject of continuing investigation and will be reported on in a supplementary document. In addition, acute exposures are assumed to occur at levels at least 10-fold higher than average low level "background" exposures. If these conditions are not met, a complex exposure pattern exists that is not amenable to assessment using these methods. These assumptions are made to allow individual exposures to be treated as if they are independent of each other and independent of lower-level long-term exposures. Acute exposures should be evaluated with respect to what is known about the time course of development and repair of the health effects and the persistence of the chemical in the body.

28. Current approaches for noncancer dose-response assessment for inhalation exposure at U.S. EPA principally focus on chronic (lifetime) exposures and the derivation of a Chronic RfC. The current definition of the Chronic RfC (U.S. EPA, 2006) is "an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark concentration, with uncertainty factors applied to reflect limitations of the data used."

Acute RfC Definition

29. This Preliminary Methodology Document, in accordance with the RAF guidance (U.S. EPA, 2002), proposes to adopt a similar definition for the Acute RfC:

> "An estimation (with uncertainty spanning perhaps an order of magnitude) of an inhalation exposure for an acute duration equal to or less than 24 h to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It is derived from a

> BMCL [lower confidence limit on a benchmark concentration], a NOAEL, a LOAEL, or another suitable POD, with uncertainty/variability factors applied to reflect limitations of the data used."

30. The Acute RfC is best regarded as a ceiling value which should not be exceeded during any interval of time for the designated duration. It is **NOT** to be interpreted as a time-weighted average. There should be adequate information provided in the Toxicological Review document for an Acute RfC to derive appropriate values for durations other than those provided in the assessment, if necessary to do so.

31. As already discussed, another aspect to consider in developing and utilizing an Acute RfC is that an individual should not be exposed to another "concentration-above-background" for the subject chemical until after an adequate recovery period. Acute RfCs should be considered health protective for intermittent exposures equal to or less than 24 h; if the duration exceeds that limitation and/or an adequate time for recovery cannot be met, a longer duration reference value (i.e., Short-term, Long-term, or a Chronic RfC) should be applied. The subject of defining an adequate recovery period is not addressed in this document but is intended to be included in supplements and in the final methodology.

32. In this document and in the example assessments (EtO, HCCPD, H_2S, and phosgene), values are developed for 1-, 4-, 8-, and 24-h durations, when possible. The Acute RfC, however, may be derived for other durations (within limitations of the available data). Also, based on the available data, values for some of the durations previously noted may not be possible to derive.

33. A causal relationship, or at least an association between exposure concentration and response, needs to be reasonably established before such information can be considered as dose-response information and utilized as such. The range of exposure-related effects include immediate changes (such as decreases in breathing rates in response to increasing chamber concentrations of a toxicant), effects not immediately apparent (such as pathological changes becoming manifest after the single exposure), or alterations that may be considered delayed or latent (such as neurotoxicity when the effect is not observed until several days after the exposure). Thus, information on delayed effects from acute inhalation exposures should be incorporated when it is available.

34. A fundamental property of any methodology is flexibility such that it can be used as a general approach for a large number of chemicals with a wide range in the quantity and quality of toxicity data. The method for derivation of the Acute RfC employs several different approaches to quantitative assessment, with the choice of approach for any chemical being determined by the extent and quality of data for that chemical to maximize the use of all available data. This document attempts to search out and accommodate flexibility through the performance of example applications for four chemicals: EtO, HCCPD, H_2S, and phosgene. All four of these acute assessments are discussed in general in this document. The general discussions in this document will highlight available dose-response approaches (e.g., BMC, categorical regression, NOAEL/NOAEL) as they are appropriate for the existing database. The detailed assessments (i.e., the IRIS Toxicological Reviews) include summaries of relevant toxicological studies, displays of data, choices of dose-response methods, application of UFs, and calculation and characterization of the Acute RfC with respect to strengths, limitations, and uncertainty.

35. In most cases, the Acute RfC will be derived based on animal toxicity or possibly human clinical experiments performed under controlled conditions of a single exposure to an otherwise unexposed subject. With the exception of rare events, such as spills or accidents, actual exposures will differ from the experimental exposures in two important ways. These differences could introduce constraints on the applicability of the Acute RfC to some human exposure scenarios. First, real-world short-duration exposures may occur on an intermittent basis, rather than as rare events. This ambient scenario introduces the possibility of cumulative effects, which would not be predicted by the single-exposure experimental protocol. Second, a single exposure below the exposure evoking an adverse effect could result in changes that increase the susceptibility to subsequent exposures (e.g., depletion of some protective mechanism). It is theoretically necessary for such changes to be resolved, and the dose completely cleared, prior to a subsequent exposure in order to assure that the response to the subsequent exposures is not increased, or otherwise influenced, by the previous exposure. Very few, if any, chemicals will have adequate data to

allow a confident determination of the "safe" periodicity of an acute exposure, so the basis is limited for generalization about the appropriate application of the term "intermittent" in the definition of the Acute RfC.

36. In some cases, estimating levels of exposure other than those resulting in no adverse effect has value. The development of chemical emergency planning guidelines usually yields three different exposure levels, which are defined by the severity of the predicted effect (i.e., mild, severe, or life-threatening) (National Research Council, 1993; Rusch, 1993; Craig et al., 2000). Exposure levels expected to produce adverse effects could require greater intervals between exposures to prevent cumulative effects than would exposures producing no effects. The Acute RfC method is amenable to these applications, given adequate data. The intent of this document, however, is to provide approaches for developing benchmarks that produce no adverse health effects.

1.2.1 Relationship of Acute RfCs to Other Acute Inhalation Reference Values

37. The procedures described within this document are intended to estimate exposure levels that produce no adverse effects in sensitive humans so that those levels may be used to determine the noncancer health risks (by the hazard quotient/hazard index methodology) of acute (≤24-h) inhalation exposures. Other nationally recognized methods to develop acute inhalation exposure limits for the general population are focused on developing levels for screening purposes or for chemical emergency planning uses.

38. Minimal Risk Levels (MRLs), developed by the Agency for Toxic Substances and Disease Registry (ATSDR), are used as screening levels to identify contaminants and potential health effects that may be of concern at hazardous waste sites (ATSDR, 2005). MRLs, which are intended to protect the general population, including sensitive humans, are estimates of daily human exposure likely to be without appreciable risk of noncancer health effects for a specified duration of exposure. For development of MRLs, an acute duration is defined to be 1 to 14 days. MRLs are used as a screening tool by public health professionals to help decide where to look more closely and to identify those hazardous waste sites not expected to cause adverse health effects. In contrast, Acute RfCs are associated with more narrowly defined, single, continuous exposures and are intended for use in estimating noncancer risks to acute inhalation exposures (equal to or less than 24 h).

39. Other acute inhalation exposure limits that protect the general population include certain chemical emergency planning values. The American Industrial Hygiene Association, which established a committee to develop ERPGs, pioneered the concept of developing three different airborne concentrations for each chemical, defined by the severity of the predicted effect (Rusch, 1993). Other groups (National Research Council, 1993; Craig et al., 2000) working in the area of emergency response planning have used similar three-level schemes, because the action taken in response to an emergency varies depending on whether a mild, severe, or life-threatening effect is predicted. One of the most active developers of chemical emergency planning guidelines, the NAC/AEGL, uses Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances (National Research Council, 1993) and the Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals (National Research Council, 2001), as guidance for AEGL development. The procedures within this document are intended to be amenable to these applications, given adequate data. However, the intent of the procedures described in this document differs from that of emergency planning, and more health-protective benchmarks are likely to result from these procedures. Toxicity benchmarks for emergency planning tend to be less protective than those for health risk assessment, because although they must be low enough to protect most of the potentially exposed population, they must also be high enough to minimize false alarms and overresponse (National Research Council, 1993).

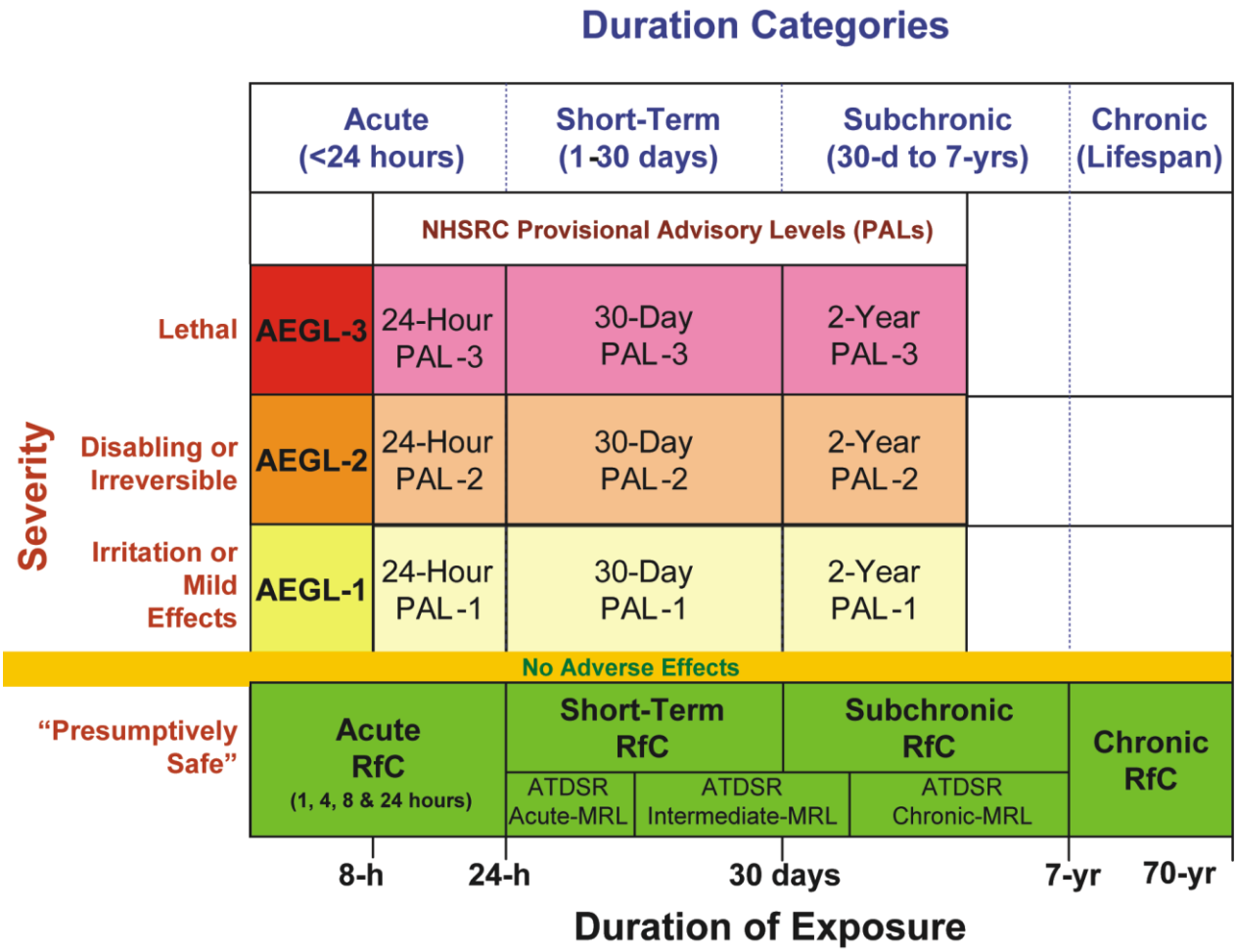

Figure 1-1. Comparison of AEGL, PAL, and ATSDR MRL values to the Acute, Shortterm, Subchronic, and Chronic RfC based on severity and duration.

1.3 General Principles of Health Assessment for Noncancer Endpoints

40. General principles of noncancer toxicity have been reviewed by the U.S. EPA (1994a) and IRIS (1993) and will not be discussed in detail here. A few points relevant to acute noncancer toxicity are mentioned briefly.

41. Most toxicants cause effects in several organs, although one effect might predominate. It should be kept in mind that the major target organ (or the most sensitive target organ) can differ between species, as well as within a species, with different exposure scenarios. Thus, the study that uses a species having mechanisms most similar to humans and is most similar to the exposure scenario of interest would ideally be used to develop the Acute RfC.

42. Exposure is not the same as dose. Although this important principle has been receiving more attention in the contexts of chronic cancer and noncancer risk assessment, its importance in evaluating acute exposures cannot be overemphasized. For chemicals that equilibrate with the body during exposure, the most rapid changes in internal concentration and internal dose in a given species occur in the first minutes to hours of exposure. Thus, any potential interspecies or interindividual differences are most apparent when the exposure duration of interest is near or shorter than the time required for the exposure environment to reach equilibrium with the internal environment. Allometric relationships based on body weight for the various determinants of dose among species are predictive of such situations. For example, the species relationship for ventilation rates, a major determinant of dose, is that smaller animals will have

higher breathing rates than larger animals such that for a given air concentration of an agent, equilibrium will be attained in the smaller before it is achieved in the larger animal.

43. The most important concept related to noncancer assessment is the assumption of the existence of a threshold. For the purpose of this document, the threshold exposure is defined as the exposure below which an adverse effect is not expected. As will be discussed, the definition of threshold can also be applied to various categories of effect (e.g., the threshold for mild adverse, moderate/severe effects, or lethality). Estimation of the threshold, or subthreshold, exposure becomes the object of the dose-response assessment. Thus, the definition of the threshold, either as a general concept or as a specific level of exposure for a particular chemical or endpoint, assumes a high level of importance in any noncancer assessment. The definition of threshold is complicated because it includes elements of the end use of the assessment (e.g., legislative mandates and implementation policy) as well as elements of data interpretation (e.g., power of a given study to detect an effect, adverse or otherwise; individual versus population thresholds) and science policy (e.g., questions of adversity, severity, and biological versus statistical significance). Also, the range over which extrapolations are performed is affected by the assumption of a threshold when the location or even existence of the threshold is more often not known.

1.4 Current Health Assessment Methods for Noncancer Effects

44. The underlying basic concepts of dose-response assessment within the chronic RfC methodology are intended to be reflected in this Preliminary Methodology Document and in all future installments leading to a formal Acute RfC Methodology. As indicated in their respective definitions (Section 1.2 of this document), both build on established Agency practices such as the use of the NOAEL or BMD/C methods as a POD for dose-response assessment, and the application of UF to derive a toxicity benchmark.

45. A principal and vital contrast between the Chronic RfC and the Acute RfC is that of duration. As the chronic RfC is clearly stated to involve lifetime continuous exposure, considerations for duration are not relevant, its only accommodation for duration being the "subchronic to chronic" extrapolation UF. In the acute exposure scenario (i.e., ≤24-h), duration of exposure is a major and critical determinant of response. This criticality has long been recognized and applied through Haber's relationship (often referred to as "Haber's Rule"), where the concentration of an agent (C) multiplied by the time/duration of exposure (T) equals a constant (k): $C \times T = k$. More recently, ten Berge et al. (1986) have offered a more adaptable variation on that equation by placing an exponent (n) on the concentration term to yield the formula $C^n \times T = k$. As Acute RfCs for different durations (e.g., 1-, 4-, 8-, and 24-h) are principal outcomes of this document, major portions of this Preliminary Methodology Document are dedicated to examining and demonstrating the use of various approaches to duration extrapolation.

46. Acute RfCs may be anticipated to be higher in absolute values (actually air concentrations) than the corresponding Chronic RfCs, as the ≤24-h exposure duration for acute exposure are greatly reduced compared to lifetime continuous exposure. Further, due to the range of possible exposure durations that may fit within the Acute RfC definition, from 1 h up to 24 h (with possible calculation to shorter durations, depending on need), Acute RfCs require definition in terms of both concentration and specific duration, a situation not at all applicable to the Chronic RfC. Sections 2.1.1 and 2.3.2 will provide more information and analysis on the importance of exposure duration.

1.4.1 No-Observed-Adverse-Effect Level (NOAEL) Approach

47. This approach is primarily based on the selection of the appropriate experimental exposure at which no adverse effect is observed. Ideally a NOAEL (or if one is not available, the corresponding LOAEL) is chosen from an array of dose-response information (usually for a single duration) such that the most sensitive NOAEL can be recognized and chosen. The adverse effect associated with the lowest NOAEL is regarded as the critical effect (i.e., that which occurs at the lowest exposure concentration and, in the case of the Acute RfC, with consideration of duration). The NOAEL for the critical effect may be regarded as the POD and used further in the quantitative assessment. Dosimetric adjustment procedures may then be applied to the POD to convert the exposure concentration of the NOAEL in laboratory animals to an HEC to derive a $NOAEL_{HEC}$. UFs are applied to the $NOAEL_{HEC}$ to derive the Acute RfC. If a NOAEL is not available, the lowest $LOAEL_{HEC}$ is used, with the addition of a UF for extrapolation from

an effect level to a NOAEL. UFs may be applied for a number of other extrapolations including animal to human (a residual uncertainty from derivation of an HEC), intrahuman variability, and residual "database" uncertainties (for "extrapolation" to a complete database). This approach (referred to in this document as the NOAEL approach) is also used to derive the RfD for chronic oral exposure, and 1-, 10-, and 90-day health advisories for drinking water (Ware, 1989) for shorter duration oral exposures. A major criticism of the NOAEL approach is that its reliance on a single data point as the basis of the derivation does not allow for explicit consideration of the shape of the dose-response curve, the number of animals in the group, or the statistical variation in the response and its measurement. That the NOAEL is chosen from an array of all available data serves to offset this criticism somewhat.

1.4.2 Benchmark Concentration Approach

48. Mathematical concentration-response modeling can be used to predict a response level that will serve as the initial basis of a health assessment. Since Crump (1984) proposed the "benchmark dose," or BMD, method, there has been a great deal of interest and an increasing level of activity, exemplified by an RAF document on the approach (U.S. EPA, 1995), the continuing effort of the U.S. EPA to develop guidelines for use of BMD, and the development of U.S. EPA software for implementing the approach (U.S. EPA, 2000b,c). The approach for the inhalation scenario, termed the benchmark concentration, or BMC, refers to fitting a mathematical model to a data set containing multiple concentration levels (with each set nearly always limited to a single duration) and selecting a predetermined response (or level of risk) as the benchmark risk (BMR). The lower bound on the concentration (the BMCL) predicted by the model to cause the defined response, or risk, is then divided by UFs. Compared to the NOAEL approach, the BMC method has the advantages that it does not require application of a UF when a NOAEL does not exist, it directly and quantitatively utilizes more information from the concentration-response curve (e.g., slope), is less influenced by experimental design (e.g., dose spacing), and is sensitive to the influence of sample size. In addition, the BMC can consider the variability of the response in the experimental population when a continuous variable (e.g., respiratory rate) is modeled (Crump, 1984, 1995; Dourson et al., 1985). The BMC approach has been applied to the derivation of several Chronic RfCs, for a variety of toxic endpoints, included in the IRIS database (U.S. EPA, 2006).

1.4.3 Categorical Regression Approach

49. Conceptually distinct from the NOAEL and BMC methods for evaluating exposure-response data are approaches for analysis of categorical or ordinal data. One approach is regression analysis of response data categorized by severity. For this approach, effect data from the toxicological literature are assigned to severity categories (e.g., no effect, mild effect, and severe effect) based on evaluation of the reported information and consideration of biological and statistical significance. This categorization allows incorporation of both dichotomous and continuous data, as well as data that are reported qualitatively, into the analysis. The data in this form can be analyzed for single studies, for combinations of studies based on a particular designation (e.g., species, sex), for all studies for a particular chemical simultaneously, or most importantly, to generate a concentration-duration relationship.

50. The application of a categorical regression method (McCullagh, 1980) to risk assessment was first proposed by Hertzberg and Miller (1985) and further defined by Hertzberg (1989) as a way to empirically derive an interspecies extrapolation factor. Subsequently, this approach was suggested as a method for chronic exposure-response assessment that would allow a general description of the exposure-severity relationship, as well as estimation of the risk of adverse effects at exposures above the RfD, but below the range of doses that have been studied experimentally (Knauf and Hertzberg, 1989; Dourson et al., 1997). It was noted in the initial papers describing this application that the inclusion of other independent variables, such as exposure duration, would be possible using this model. The severity-based approach and the CatReg software (U.S. EPA, 2000b) developed for this purpose has been applied to exposure-response analysis for acute inhalation exposure and to examination of the role of concentration and duration of exposure (Guth et al., 1991, 1997; Guth, 1996) in producing adverse effects.

1.4.4 Other Approaches

51. In addition to categorical regression, several other approaches to combining quantitative data from multiple studies have been developed. In most cases, these approaches combine results from similar

studies (meta-analysis), although dissimilar studies also have been combined. These approaches also rely on the availability of information reported at the individual subject level, because they are combining estimates of the effect or parameter of interest and the variance of the effect or parameter.

52. Meta-analytical approaches may also lead to a POD for deriving RfCs for any duration. The example assessment for ethylene oxide (short-term) demonstrates how results from BMC analysis on several studies for a single critical endpoint may be combined to derive the POD.

53. A Bayesian approach has been proposed to use the concentration-response curve of individual studies, while incorporating variability in the response measure and combining response data from individual studies (Jarabek and Hasselblad, 1991; Hasselblad and Jarabek, 1996). In this approach, a level of response for a particular health effect is specified and the probability distribution of the health effect as a function of concentration is derived. This part of the analysis is analogous to deriving the confidence envelope around the BMC estimate. This distribution is combined with other information, such as the distribution obtained from a second study (termed "priors," or prior information) using Bayesian statistics to obtain a "posterior," or combined, distribution. This process can be repeated until all relevant studies are incorporated. Like the BMC approach, this approach requires quantitative data and is not amenable, in its present form, to analysis of categorical data. At this time, the approach is still under development and, therefore, has not been adopted for use in development of Acute RfCs. However, the Bayesian approach has potential applicability to acute health effects and will be considered as an adjunct to the method for derivation of Acute RfCs in the future.

1.4.5 Approaches to Dose-Response Analysis in the Development of an Acute Reference Concentration

54. Because the programmatic need is to evaluate acute effects for as many chemicals of interest to U.S. EPA as practicable, given some minimum data set below which evaluation cannot be attempted, it is not appropriate to restrict the level of the analysis too narrowly. Doing so would eliminate the option of carrying out an analysis for some chemicals and not make good use of the available data for others. Based on these considerations, Acute RfC development is designed with a choice of several methods (e.g., NOAEL, BMC, categorical regression) each with different data requirements. As discussed above, the approach used should be matched to and dictated by the data available for a particular chemical so as to optimize the use of the data. The selection of the most appropriate approach in a given situation is not clearly defined and will depend on a number of factors that are discussed in Section 2.

55. The three approaches recommended for Acute RfC development are NOAEL, BMC and categorical regression. The methods making use of mathematical dose-response models, BMC and categorical regression, are preferred when the toxicological data are sufficient to support these methods. Dose-response models are preferred to the NOAEL approach, because they use information from the entire dose-response curve rather than from a single experimental point. Three other advantages of the BMC approach are that (1) it is less sensitive to dose spacing than the NOAEL approach, (2) it is more sensitive to group size than the NOAEL approach, and (3) it does not require the application of a UF when a NOAEL does not exist. The three major advantages of categorical regression in comparison to the other two methods are (1) continuous, dichotomous, and descriptive data can be used simultaneously; (2) data from many studies can be combined; and (3) a quantitative concentration-duration relationship is developed. Both BMC and NOAEL approaches use only one primary study to develop the Acute RfC, and a toxicity benchmark for only one duration is identified. Disadvantages of categorical regression include the loss of quantitative information, which occurs when response data are categorized into severity categories as well as the inherently subjective judgment of severity categorization. The NOAEL approach, which is the most commonly used method to develop toxicity benchmarks for noncancer effects, is recommended for use as a default method for Acute RfC development when the available acute toxicity data will not support the use of a dose-response model.

1.5 Approaches to Duration Extrapolation

56. Both exposure concentration and exposure duration are principal determinants of the toxic response under the acute exposure scenarios this Preliminary Methodology Document is intended to address. The criticality of the exposure duration relationship under acute scenario conditions is

exemplified by considering an example of direct application of Haber's relationship, C × T, to durations under consideration for reporting as Acute RfCs (e.g., at 1-, 4-, 8-, and 24-h). For a given toxic agent, a 1-h Acute RfC at 100 ppm would be extrapolated to 25 ppm at 4 h, 12.5 ppm at 8 h, and 4.2 ppm at 24 h. Such marked differences in Acute RfC values for the same toxic agent requires careful and thorough consideration by whatever means available to the assessor.

57. As the internal dose is the ultimate determinant of risk, factors determinative of the internal dose at the target site (i.e., exposure concentration and exposure duration) become equally critical. The dose at the target tissue will depend not only upon the amount deposited or absorbed but also on the clearance rate or rate of activation or inactivation, depending on the MOA. Because they can provide a correlation of the internal dose to the response under these conditions, physiologically based pharmacokinetic (PBPK) models can be used for establishing the exposure concentration-duration relationship and this Preliminary Methodology Document endorses the use of properly parameterized PBPK models for such purposes.

58. 57. Although more PBPK models are now becoming available, there are relatively few compared to the vast number of toxic agents that will be under consideration for RfC development. In lieu of such models, exposure-duration C × T relationships have been most often characterized by mathematical constructs from empirical observations. Historically, the most commonly used relationship has been Haber's relationship which suggests that the product of these determinants is a constant, $C \times T = k$. Haber's relationship is often viewed as a special case of the more generalized relationship empirically derived by ten Berge et al. (1986) wherein the concentration/duration-time model is expressed as $C^n \times T^b = k$, with *n* and *b* being empirically derived. It should also be noted that the majority of data that has been utilized in these analyses is chemical-specific mortality data. This Preliminary Methodology Document recognizes these options for determining the concentration-duration relationship.

59. In addition, this Preliminary Methodology Document presents and provides examples in the use of categorical regression as an alternate option of determining the concentration-duration relationship using chemical-specific information that may not be mortality data. The capacity of categorical regression (or CatReg, the Agency's version of categorical regression), to provide concentration-severity relationships has been discussed above. This capacity to derive concentration-severity relationships has been expanded within the CatReg program to provide quantitative concentration-severity relationships over duration/time of exposure. Further, these relationships may be defined from chemical-specific information for severities other than the highest (i.e., mortality). From inputs of information on different severity levels, exposure concentrations, and durations, CatReg outputs can be made to assume the form of concentration-duration relationships for individual severity levels. Concentrations associated with specific severity levels at specific durations can then be obtained from these concentration-duration plots. Alternatively, the parameters defining the shape or slope of the concentration-duration plots may be applied to an independently derived POD, such as a BMC estimate.

2. DEVELOPMENT OF AN ACUTE INHALATION EXPOSURE-RESPONSE ASSESSMENT

60. This chapter of the Preliminary Methodology Document focuses on the various steps necessary to develop an acute inhalation exposure-response assessment, and will delve into the detailed considerations needed to perform each of those steps. Specific aspects of the process will be illustrated by the examples performed in support of the acute inhalation method development process, which are discussed in general in Section 3 and presented in full detail in the individual IRIS Toxicological Reviews for the four example compounds (EtO, HCCPD, H_2S, and phosgene). Figure 2-1 provides a stepwise decision tree that is designed to guide a risk assessment professional through the process of developing an assessment of health risk from acute inhalation exposures. Each step along the way in this graphic depiction of this process also refers to a section in this chapter that provides greater detail on that particular step of the process.

2.1 Collection and Evaluation of Relevant Data

61. Health assessments must be based on a complete review of the toxicological literature. The available inhalation data will vary for individual chemicals, exhibiting a wide range in the number of studies, the number of exposure levels and durations studied, and the range of endpoints examined. In general, there tend to be many more studies using acute or short-term durations than using subchronic to chronic exposure durations. In many cases, however, acute inhalation studies focus on mechanisms, pathogenesis, or pharmacokinetics without evaluating exposure-response relationships. In these cases, information on the effects that might have been observed is not necessarily critical to the main point of the study and may not be reported in detail, making it important to judge whether and in what way the information is useful. Information from these types of studies may be relevant and useful even if they are not focused on exposure-response relationships. Another consideration is that quite a few studies may focus on a single effect (e.g., lethality) or on a few organ systems and miss effects on other potentially sensitive organs.

62. There is also a range of exposure-response data types found in acute inhalation studies. Dichotomous (incidence), continuous (measurements on a continuum), and categorical (descriptive) variables are commonly reported. Categorical effect measures are frequently encountered in the toxicological literature in descriptions of histological observations, and in some cases, effect information is limited to relative severity.

63. Many guidelines, methodologies, and discussions of risk assessment approaches contain a background discussion of general criteria for evaluating the quality of studies, including the *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994), and the *Guidelines for Developing Community Emergency Response Exposure Levels for Hazardous Substances* (National Research Council, 1993). These criteria will not be repeated here.

64. All available literature describing health studies having acute exposures should be reviewed with the goal of including all studies in the analysis with clearly defined exposure concentrations, exposure durations, and responses. Whereas it is perennially true that more information is better, the Acute RfC approaches proposed in this Preliminary Methodology Document have basic data requirements for deriving meaningful exposure-response-duration relationships from acute toxicity data. The quantity of information available is pivotal in deciding which of the approaches (e.g., NOAEL, BMC, categorical regression) should be used for quantitative analysis. To help distinguish the NOAEL, BMC and categorical regression approaches, Table 2-1 characterizes the data requirements for each. The data requirements are divided into computational and interpretational requirements. Data required for computational purposes are those necessary to compute a numerical POD. Data required for interpretational purposes are those required to interpret the POD, and to then apply it in the subsequent steps of an Acute RfC derivation.

65. Of the three approaches, only categorical regression explicitly uses exposure duration for computational purposes. The NOAEL and BMC approaches, however, require exposure duration (as in X mg/m^3 at Y h) for proper interpretation and use. How this information is used is discussed in Section 2.6.3.

66. Severity data is required for computation during categorical regression analysis, but is most infrequently specified in the literature directly. Histopathology data frequently does have severity scores or lesion grades accompanying the lesion description. Most often, however, the severity category has to be considered and assigned by the assessor through analyzing and making judgments on the continuous or incidence data available. Decisions made on severity should be clearly identified, reasonable, defensible, and in line with the general guidance given in Table 2-1. For judgment on a continuous parameter such as decreases in nerve conduction velocity, for example, consultation with neurotoxicologists may be necessary for professional opinions on what level of decrease is within the background levels or is marginally or clearly adverse. The outcome of such a consultation would form the basis for determining ordinal severity (i.e., the conversion of continuous data into categorical data) and should thus be carefully and clearly documented.

67. In general, data should be captured for every experimental exposure concentration tested (including controls), along with details of the duration of exposure, measurements of the response levels for each parameter measured (i.e., there may be more than one measure for a single endpoint and/or more than one endpoint measured), and any other pertinent details related to exposure conditions. The example assessments illustrate the widely varying and assorted types of information and level of detail amenable to analysis.

2.2 Evaluation of Endpoints

68. Once it is determined that a study is of adequate quality for inclusion in the assessment (e.g., the methods are appropriate to the endpoint, dose-response and duration information is provided in a format amenable to analysis, the informed opinion of the assessor), it is necessary to determine the relevance of the specific endpoints. For example, acute exposures are often used to evaluate mechanisms of toxicity or pharmacokinetics, rather than exposure-response-relationships. Such studies are very useful in interpreting the available data, but they are ineligible for dose-response assessment purposes if the endpoints examined cannot be clearly related to a toxic effect. A few endpoints have been determined to be qualitatively irrelevant to human health assessment, because they act through mechanisms that do not exist in humans, for example, male rat kidney lesions caused by chemicals that increase production of $alpha_{2u}$-globulin (U.S. EPA, 1991).

69. The quantitative derivation of Acute RfCs by the BMC and NOAEL approaches should focus on sensitive endpoints (i.e., toxic effects that occur at relatively low exposures). Insensitive endpoints such as lethality should be used during Acute RfC development if only to assure that the exposures required to produce sensitive endpoints are sufficiently less than exposures needed to cause insensitive endpoints to assure adequate safety. In other words, how near a mild effect is to lethality in terms of exposure levels and duration.

70. In categorical regression analyses, however, data for all endpoints (sensitive and insensitive) are used to determine the intercepts of the exposure-response-duration probability curves for all severity categories and, in some models, to assist in determining the slope of the curves. Since categorical regression identifies the probability of a particular severity occurring over a range of exposure concentrations and durations, all available responses (including the least and most severe) must be included to complete the spectrum of severities that could occur. For example, in calculating the probability of rolling a three on a six-sided die, it would be inaccurate to assume the die only had five sides. Likewise, in calculating the probability of the occurrence of mild adverse effects, it would be improper to assume there were no severe adverse effects (i.e., that severe effects were impossible). In fact, output from categorical regression is given in terms of probabilities of both observing a given severity and not observing the next higher severity.

71. Regardless of the final method to be used in deriving an Acute RfC, a complete cataloging and evaluation of the dose-response-duration data is useful, and a graphical representation of the collected data available for a particular chemical, as shown in the example assessments, may prove invaluable in such an evaluation. Figure 2-2 provides some samples of the basic information that may be included in an Exposure-Response array. A graphical depiction of the information included in a database has proven to be quite useful in the example assessments. Each of the example assessments (except HCCPD) includes an

Exposure-Response array generated using Microsoft Excel to manipulate the exposure-response data stored in a Microsoft Access database (Guth and Raymond, 1996). Templates for developing these arrays are under development and have been used in the IRIS *RfD/RfC Improvement Pilot Project* and the NHSRC PAL program. Additionally, the Access database is undergoing updates and revisions. The exposure-response array may also prove useful for the development of Chronic RfCs and in cancer assessments.

72. For most chemicals, the data considered for derivation of the Acute RfC will be limited to studies of acute inhalation exposure. However, the Acute RfC method allows inclusion of developmental toxicity studies for the inhalation route. Adverse developmental effects in the fetus following chemical exposure are considered to be related to the unique susceptibility of the fetus at discrete times during gestation. The observed fetal effects result from the exposure of the pregnant dam during that particular time of fetal susceptibility. Test data having the most direct application for the Acute RfC method would be from studies in which maternal exposure occurred only during discrete periods of gestation (e.g., only gestational day 12, only gestational days 11 to 12). These single day or consecutive day studies would have the strongest linkage between a single (acute) exposure and any observed adverse effects. Where such data is available, it can easily be used in the acute evaluation. Depending on the physical and chemical properties of the chemical, some cumulative effects could occur from longer periods of repeated exposure. However, with the high potential for developmental toxicity to occur from a single exposure, it is reasonable to assume that the adverse fetal effects observed in a developmental toxicity study that includes exposures across multiple days of embryonic or fetal development, or even throughout gestation, could have occurred as the result of exposure on a single day of the study. For example, a study that includes exposures of 6-h/day on gestational days 6 through 15 will be treated for Acute RfC purposes as a single 6-h exposure to address the critical outcomes associated with developmental toxicity. This approach will, of course, always be subject to proper scientific evaluation, especially when additional information is available on pharmacokinetics or the conditions of the study that improve the understanding of the dose-response relationship. Some of the issues related to the use of repeated exposure developmental studies and how well they compare to similar single exposure developmental studies are reviewed by van Raaij et al. (2003).

2.2.1 Adversity and Severity of Effects

73. The interpretation of the adversity of noncancer effects is one of the most difficult aspects of noncancer risk assessment. The U.S. EPA defines adverse effects to be "functional impairments or pathological lesions that may affect the performance of the whole organism or that reduce an organism's ability to respond to an additional challenge" (U.S. EPA, 1994; IRIS, 1993). In large part, the difficulty in the determination of adversity stems from the need to interpret specific biochemical, anatomical, or functional changes in terms of their importance to a higher level of organization, the whole animal. The use of increasingly sophisticated methods to detect subtle changes makes the determination of adverse/not adverse an ever-increasing challenge.

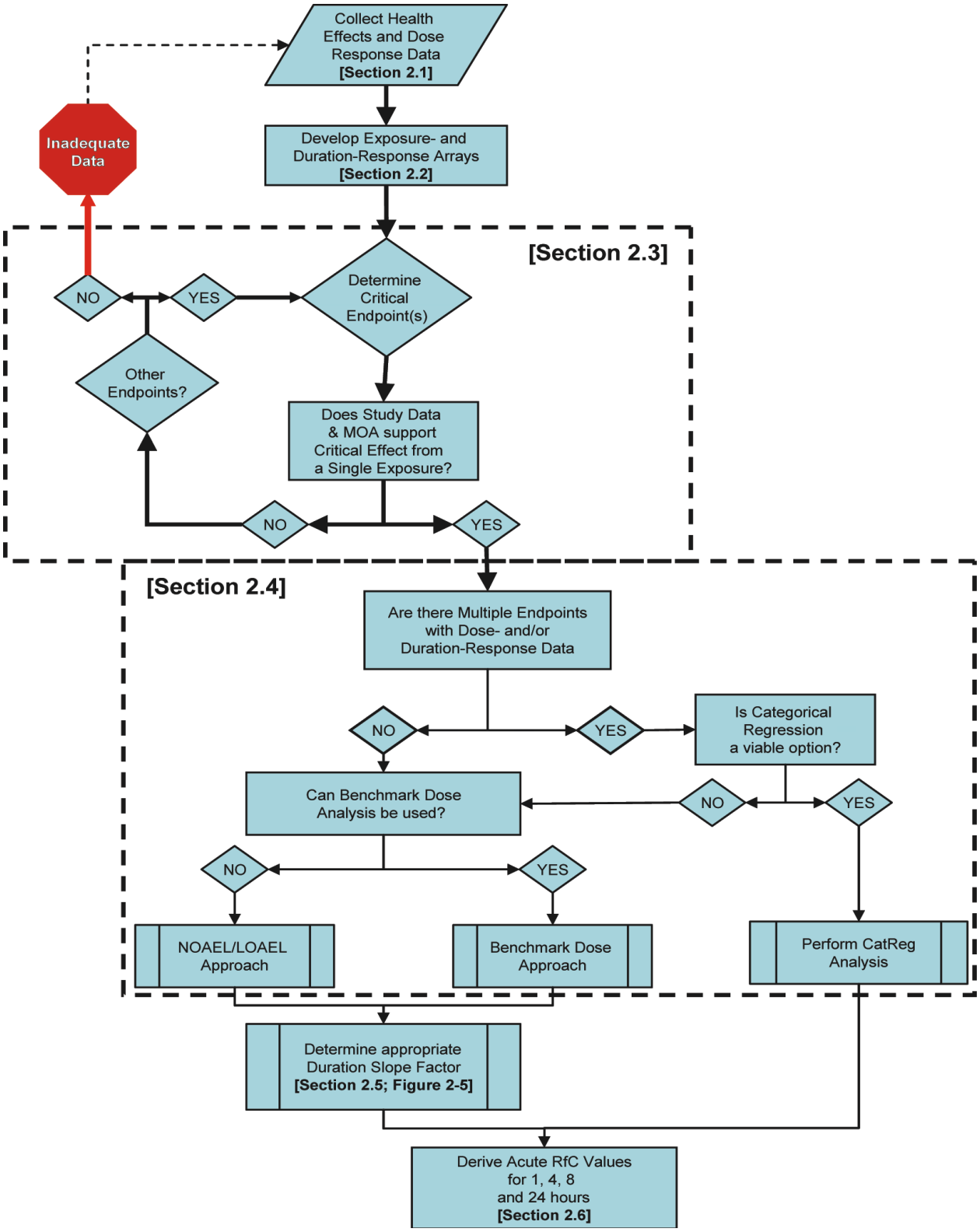

Figure 2-1. Decision tree for performing an acute inhalation exposure-response assessment 2-1.Decision tree for performing an acute inhalation exposure-response assessment.

Table 2-1. Acute Reference Exposure Computational (C) and Interpretational (I) Data Requirements

Variable	*Approach*		
	Categorical Regression	*BMC*	*NOAEL*
Exposure Concentration	*C*	*C*	*C*
Exposure Duration	*C*	*I*	*I*
Effect Data			
severity category	*C*	*I*	*I*
incidence	*	*C*	*C*
continuous	*	*C*	*C*
Species/Strain	*I*	*I*	*I*
Group Size	*I*	*I*	*I*
Sex	*I*	*I*	*I*

**Incidence or continuous measure data may be needed for determination of severity category, but they are not necessarily categorical in nature by themselves.*

74. Severity has been defined as the extent to which an effect impairs the functional capacity of an organism (U.S. EPA, 1989), i.e., the degree of adversity. This definition reflects the fact that almost all toxicity is expressed and observed as a graded series of changes, with severity, in some cases, used to describe the general location on the continuum of response. This continuum is a composite of many variables, including amount, magnitude, location, incidence, reversibility, measurability, and other factors that give an indication of the severity. If severity is seen as the continuum of biological response, then adverse responses are defined as that point on the continuum where the criteria for adversity are met. Based on the definition cited in the previous paragraph, the criteria for adversity are that the "performance of the whole organism" or the "ability of the organism to respond to additional challenges" is diminished.

75. The key variables that define severity were characterized as "type" of effect and "magnitude" of effect (U.S. EPA, 1989), reflecting the common distinction between qualitative and quantitative aspects of toxicity. Qualitatively, effects can be ranked in terms of their severity. For example, necrosis of nerve cells in the brain is more severe than necrosis of liver cells, because liver cells can regenerate more readily, but liver necrosis is more severe than fatty changes in the liver. The magnitude can be considered separately, in that all toxic effects are assumed to increase in magnitude as a function of dose. However, the aspects of type and magnitude of effect cannot be completely separated, because widespread occurrence of a qualitatively less severe effect could be of more public health concern than focal occurrence of a more severe effect and because an increase in magnitude with increasing dose is often accompanied by a qualitative progression in the nature of the effect.

76. Ranking or scaling of effect severity is a critical component of the categorical regression approach. It is, however, not discussed in detail in this Preliminary Methodology Document. The

interested reader is directed to the discussion of this topic in the Agency's CatReg User's Manual (U.S. EPA, 2000d), and additionally refer to the current example acute assessments in which CatReg is utilized, namely phosgene and hydrogen sulfide.

Defining Adversity for an Endpoint

77. The determination of whether a response is adverse for a particular endpoint is the most important judgment for the use of that endpoint in noncancer risk assessment and can be the most controversial. The designation of reported effects as adverse or not adverse requires a judgment as to the magnitude or severity of effect that is adverse for the endpoint under consideration. Although not determined in the absence of other information, it is reasonable to assume in most cases that the criteria for adversity are target-organ specific and chemical independent. These criteria are rarely made explicit, with a few exceptions, such as the informal use of a 10% lower body weight or 2% decrease in brain weight in exposed groups as a determinant for adversity in a chronic study. If it is possible to determine adversity, then it is possible to state the minimum level of response that is adverse. For derivation of the Acute RfC, the level of response that is considered adverse must be explicitly documented and may or may not correspond to what was reported by the study authors.

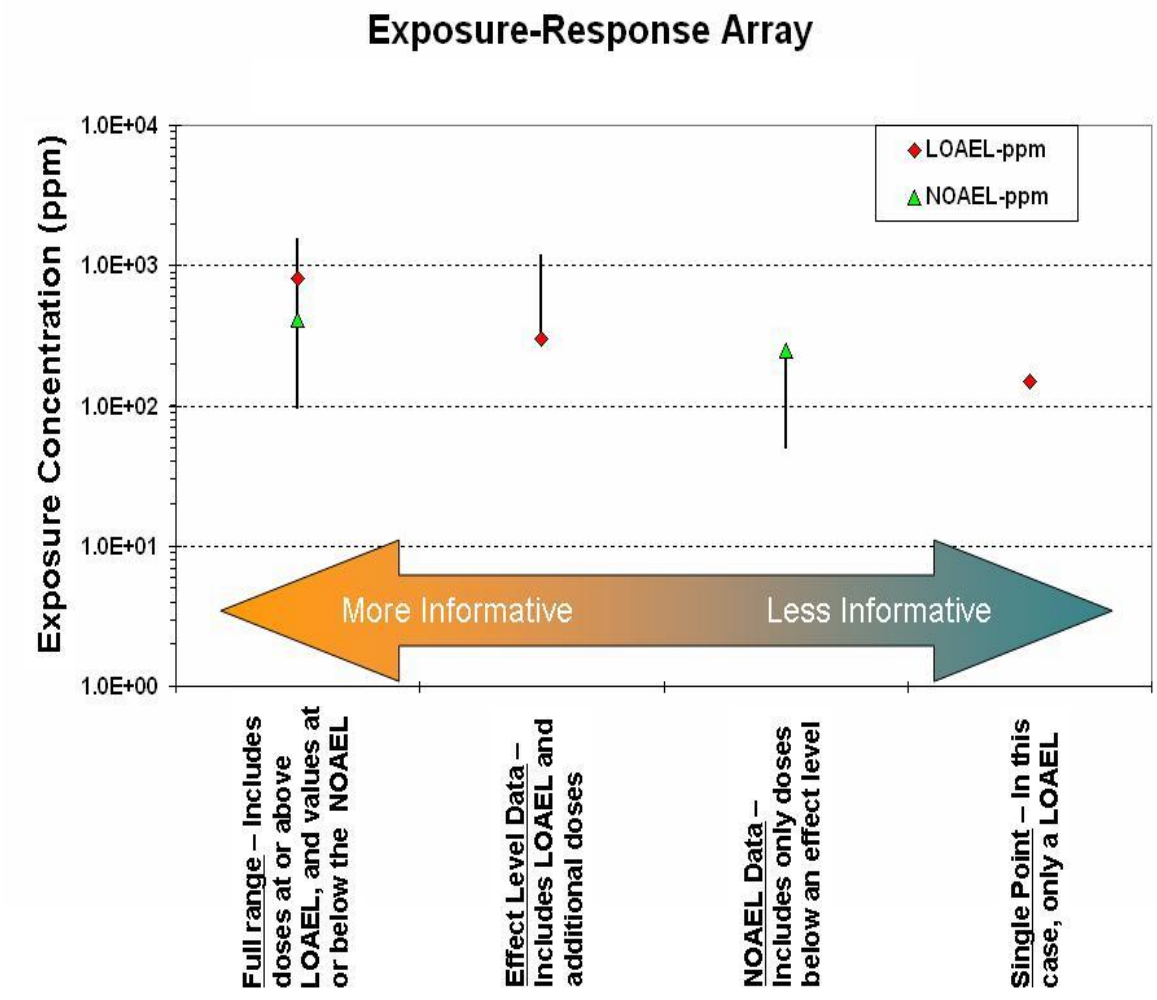

Figure 2-2. Introductory description of an Exposure-Response Array and the graphic depiction of the level of detail for individual study data.

Statistical Versus Biological Significance

78. Adversity of effects has previously been defined based on biologically and statistically significant changes compared to controls. This language reflects the understanding that it is possible to observe statistically significant changes that are biologically unimportant, and conversely, to observe biologically important effects that are not statistically significant.

79. In practice, statistical significance plays a major role in determining adversity, especially when there is a limited basis in biology for a judgment. This practice introduces complexity into the decision on adversity, because the same magnitude of response could be considered statistically significant or nonsignificant, depending on the number of subjects in the groups, variability in response, and other design elements such as the statistical test and p-value used to define significance. If a study is scientifically sound from all aspects, statistical significance in exposure-response motivates considering biological relevance. Final decisions on these issues will rest with the informed assessor. Depending on the analytical approach being taken in any particular assessment (e.g., BMC or categorical regression), additional guidance may be available from the technical guidance and/or user's manual.

Designation of Adverse Effect Levels

80. For the NOAEL and categorical regression approaches, the designation of severity categories for health effect data proceeds as part of the quantitative analysis. The determinations made are based on comparison of the reported effects with the magnitude of effect consistent with the onset of adversity, although in the NOAEL approach this magnitude of effect has not been routinely identified. The BMC approach requires that a response level be explicitly defined and used to determine the BMCL. The 10% response ($BMCL_{10}$), relative to measures in a control population, has been adopted as a default BMR for dichotomous data. In the derivation of the Acute RfC, the estimates for the onset of adversity for both a $BMCL_{10}$ and a NOAEL are defined as being identical, and therefore, the model results can be interpreted as analogous. To ensure consistency, the magnitude of effect for the onset of adversity should be defined and explicitly stated and included in the documentation of the Acute RfC.

81. For the purposes of the derivation of the Acute RfC, a major and critical assumption is that a group of reasonable scientists can make judgments about this issue that are reasonably consistent across studies in a database consisting of acute toxicity studies. These judgments should be based on an understanding of the MOA and pathophysiologic continuum and outcome of the endpoints studied.

2.2.2 Generic Data Attributes for Exposure-Response Approaches

82. Although the three approaches for exposure-response analysis recommended for Acute RfC development (experimental NOAEL, BMC, and categorical regression) require different types and quantities of toxicological data, certain aspects of data evaluation are common to all three approaches. The following paragraphs discuss some aspects of toxicological data that vary when examining all available literature for a given chemical and that are relevant to quantitative exposure-response modeling. A variety of types of data are encountered that differ due to the inherent nature of the endpoint or the way the information is reported. Table 2-2 shows the types of data most often reported in the toxicological literature. Both the inherent data type and the quality of reporting determine the applicable type of exposure-response approach if additional information or raw data are not available.

83. Dichotomous data are normally reported at the individual level (e.g., 2/10 animals showed the effect). Occasionally a dichotomous endpoint will be reported as aggregate data (i.e., the incidence cannot be determined). This usually occurs when the incidence of the endpoint reported is ancillary to the focus of the report and is, therefore, not reported in detail. In this case, it may simply be stated that an effect was observed in a treatment group, with no mention of the number of animals showing the effect. Dichotomous data is amenable to analysis by the NOAEL, BMC and categorical regression approaches. For all three approaches, it must be determined whether the presence of the effect is adverse, and for the categorical regression approach, the severity of effect (i.e., the degree of adversity) must be designated.

Table 2-2. Types of Data and Reporting Most Common in Toxicological Literature

Type of Data	Aggregate Reporting	Individual Reporting
Dichotomous (e.g., dead/alive)	Presence or absence in group (no incidence)	Incidence
Continuous (e.g., body wt.)	Mean	Individual or group values – or – Mean and measure of variability
Categorical (ordinal) (e.g., descriptors such as mild/moderate/severe)	Category for the group	Incidence for each category

84. Continuous data are measurements of effects, which occur on a continuum such as airway resistance or enzyme activity. A continuous data type might be reported in several different ways, including actual measurement, absolute change from control, or relative change from control. These data may or may not be reported with a measure of variability, such as standard deviation (SD) or standard error (SE). When the measure of variability is reported, information is conveyed about the distribution of the parameter in the group, which is a reflection of the individual values. This is included in Table 2-2 as a continuous variable reported at the individual level, although it is not truly individual information. Models and technical support for application of the BMC approach to continuous data are available (U.S. EPA, 1995, 2000b,c). For the BMC and categorical regression analysis, it is necessary to define the level of effect or change for the endpoint that is considered to be adverse. The specified level of effect is used to determine the corresponding BMC and to determine severity categories for categorical regression. The level of effect so designated must be consistent with the form in which the study results are presented (e.g., absolute or relative change).

85. The measure of variability (SD/E) for a continuous variable is needed in order to use the BMC approach when the individual animal data are not available. The SD/E is also useful in helping to assign severity categories for categorical regression. In some cases in which the SD/E is not presented, the results of statistical analysis are discussed, so the inclusion of the SD/E might be considered to be conceptually redundant. Nevertheless, the lack of a SD/E for a continuous variable precludes the use of the BMC, unless partial information is presented (e.g., SD for control group only) and some assumptions are made. If neither SD/E nor statistical results are reported, then care must be exercised in assigning severity categories for NOAEL or categorical regression. The reporting of measures of variability should be noted and documented during the review of literature for the Acute RfC derivation.

86. Categorical data exist when more than one severity category can be defined in addition to the no-effect category. The treatment groups may be characterized in terms of the severity of effect (e.g., mild, moderate, or severe histopathological change). Dichotomous data can be viewed as a special case of categorical data in which there are only two categories (i.e., effect or no effect). Information might also be treated as categorical in cases where an endpoint is inherently a dichotomous or continuous variable, but is reported only descriptively, and cannot be treated quantitatively (e.g., "respiratory rate was mildly depressed in the high-dose group").

87. Health effect data may be reported for an entire treatment group in terms of severity category (aggregate reporting) or reported as the number of animals (incidence) from each group in each severity category (individual reporting). The reporting of individual versus aggregate information is a key determinant of the modeling approaches for both the BMC approach and categorical regression. While dichotomous data are normally reported at the individual level, continuous data are usually reported as a mean, with or without SD/E. BMC analysis requires individual data or aggregate data with SD/E. A categorical regression analysis can use these types of data and aggregate data without SD/E. However,

individual data are preferred, and aggregate data with SD/E can be transformed to individual data using a procedure described in Appendix A of *CatReg Software User Manual* (U.S. EPA, 2000d). For aggregate data without SD/E, the treatment group must be the unit of analysis. This is described further in Section 3 of the *CatReg Software User Manual*.

2.3 Determining the Critical Endpoint(S)

88. Once all of the dose-response data for all of the endpoints with known adverse effects from acute exposures have been collected and displayed in an exposure-response array, an appropriate critical endpoint must be selected, keeping in mind the previous discussions on adversity and severity of effects. In most cases, the endpoint chosen will be one with a study or studies showing adverse effects at the lowest exposure concentration. The assumption is that protection from those low-concentration effects will also be protective for any other adverse effects occurring at higher concentrations.

89. In making the determination of a critical endpoint, the assessors must assure themselves that the candidate endpoint can be manifested by a single exposure. For most endpoints this may seem to be a redundant consideration; however, effects from repeated exposure studies for endpoints such as developmental, reproductive, immunological, and others may require additional scrutiny, as was mentioned briefly in Section 2.2. The MOA that explains how these adverse effects manifest themselves will need to be examined to ensure that it is plausible for the effect to be triggered through a single exposure event.

2.3.1 Evaluating Level of Detail for Study Data

90. Another aspect of the analysis of data for a potentially critical endpoint is the level of detail provided to examine both the exposure concentration versus response, as well as the duration of those exposures. The preferable situation would be to have a single study design with data from multiple durations of exposure, and three or more exposure concentrations at each duration. Additionally, it is preferable to have objective clinical measurements as the response data. In the case of occupational or epidemiological studies, the response measures will often be well-characterized and target-species (human)-specific, but exposure concentrations and durations are often less well known. Conversely in many other studies, the adverse effect may be for a subjective measure (e.g., headache) that cannot be verified by an objective measure in a study with accurate exposure characterization, and this case may be just as difficult to incorporate into an analysis.

91. The level of detail available for the critical endpoint(s) will determine what types of approaches may be available to analyze a particular data set. The exposure-response array should assist in identifying the relevant studies for each endpoint with adverse health effects. The assessor should note the following for each endpoint: whether one study or a set of studies with similar study designs is available for that endpoint, and whether multiple exposure concentrations and/or multiple exposure durations are available. If either is the case for one or more endpoints (but especially for duration), the assessor should then attempt to determine if there are enough adequately detailed data with which to proceed with a categorical regression analysis (described more fully below).

2.3.2 Duration Extrapolation Considerations

92. This discussion of duration extrapolation is provided to assist the assessor in judging endpoint-specific data regarding duration. The magnitude of response to a toxic chemical exposure by inhalation is often dependent on both the concentration and the duration of the exposure. It may be that both the exposure concentration and duration actually determine the internal dose of a chemical at the target tissue and, thus, the magnitude of the response. This implies that the dose at the target tissue may depend not only upon the amount deposited or absorbed but also on the clearance rate, or rate of activation or inactivation, or some other time-dependent process related to the MOA. Thus, it is essential to consider all the mechanistic and pharmacokinetic information available for a chemical and to use that information to predict the dependence or non-dependence of the chemical's toxicity on duration. This type of information can best be used by incorporation into a PBPK model. Because they can provide a correlation of the internal measure of dose to the effect, the use of PBPK models is more scientifically defensible and desirable than default approaches. Thus, for a chemical for which sufficient pharmacokinetic information is available, use of a PBPK model is the preferred method for duration extrapolation. Once a measure of

dose (e.g., blood concentration) associated with the critical effect/response is defined, a PBPK model can be used to predict this dose metric at any exposure duration of interest.

93. Before the advent of PBPK models, response was often related to the product of concentration (C) and duration of exposure or time (T). Haber's relationship would suggest that this product is a constant, $C \times T = k$. Although widely viewed as an overgeneralization, this assumption is regularly used as a default assumption.

94. A more general version of this model advanced by ten Berge et al (1986) is expressed as $C^n \times T^b = k$, with *n* and *b* being empirically derived. Haber's relationship is actually a special case of the ten Berge model where the exponents of concentration (*n*) and time (*b*) are both unity (i.e., $C^1 \times T^1$).

95. Empirically derived values for the concentration exponent *n* in the ten Berge model have been determined for a series of chemicals with values ranging from 0.8 to 3.5 (Figure 2-3) (ten Berge et al., 1986). The endpoint typically examined to establish this relationship (specifically so in the ten Berge citation) is lethality from relatively high levels of acute exposures. Lethality and other severe consequences from exposures at the high end of the exposure/duration spectra would likely be from phenomena and mechanisms related to overwhelming homeostatic mechanisms, and as such would be accommodated and best described by this range of *n*. However, a typical POD as discussed in this document is (ideally) concerned with mildly adverse effects that are reasonably assumed to be near or within range of most homeostatic controls. It is, therefore, likely that the interposition of phenomena such as homeostasis between these extremes in severity would result in different duration-scaling relationships. It is conceivable, for example, that as the exposure (in concentration and duration) approaches the level at which the body can effectively process the chemical, the duration curve would flatten out (i.e., *n* would become larger than 3.5 and eventually approach infinity, indicating no relationship to duration).

96. Thus, in an acute exposure protocol, it is possible to observe both time-dependence (where *n* is relatively small) and time-independence (where *n* is relatively large) depending upon the chemical of interest and the nature of the internal dose underlying the response. Given the potential wide range of possible duration-dependence, a simple default such as Haber's relationship is unlikely to work well over a range of exposures to different chemicals. It is, therefore, preferable to determine the duration dependence in the exposure range of interest on a chemical-specific and endpoint-specific basis. However, for most chemicals, information on duration-dependence is largely unavailable for exposures resulting in sublethal endpoints and is sometimes unavailable even for exposures resulting in lethality.

97. Figure 2-3 shows example plots of the form $C^n \times T = k$ for various exponents based on a severe endpoint (lethality). Increased values of the exponent indicate reduced time-dependence. A value of 1 for the exponent indicates that the Haber's relationship holds and that the response is related to total inhaled dose, because exposure duration is linearly related to inhaled volume.

98. From Figure 2-3, it can be seen that $C^n \times T = k$ extrapolation from a 4-h exposure to a 1-h exposure on the basis of $n = 1$ can result in a considerably higher estimate than obtained by $n = 3$. A reasonable default is to assume a high value of *n* to extrapolate to shorter durations (e.g., $n = 3$) such that the extrapolation would yield estimates more similar to the originally observed value.

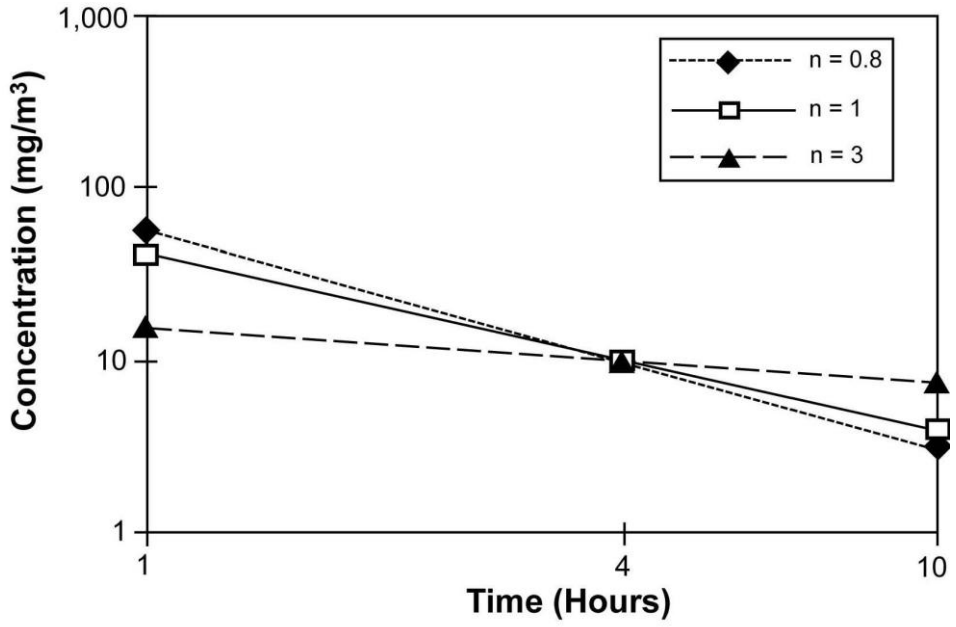

Figure 2-3. Concentration by duration plot showing the effect of the exponent in the Cn × T = constant form on extrapolation across duration.

99. Extrapolating to longer durations should require a careful consideration of all available information including the severity of the endpoint and the extent of the duration extrapolation. The analysis by ten Berge et al. (1986) based on lethality data indicates that few chemicals would be expected to show a value of $n < 1$, suggesting that at least for severe effects (i.e., those overwhelming homeostatic mechanisms as discussed above) a value of $n = 1$ would be a reasonable default for time frames longer than the observed data. It is realized from the above discussion regarding effects of lesser severity and the role of homeostatic processes that the value of n for time frames longer than the observed data may be much greater than 1 and even approach infinity. Nevertheless, in the absence of chemical-specific duration data or other scientifically defensible rationale for doing so, a value of $n = 1$ is recommended as a default for time frames longer than the observed data, regardless of the severity of the endpoint. With the realization that application of this default procedure to longer and longer durations may result in unreasonably low values, it is further recommended that extrapolations to longer times be performed with caution. In the context of this document, this means that the range of extrapolation may be limited to less than 24 hours such that derivation of a 24-h acute reference exposure value may be problematic, especially in the absence of data near this duration.

2.3.3 Judging Data Adequacy

100. Determining whether study data for any endpoint is adequate for inclusion into an exposure-response analysis will be based on the following criteria: (1) level of detail and specificity provided for the response measures, exposure concentrations, and exposure durations; (2) type of response measure; (3) adversity and severity of the endpoint; and (4) availability of adequate related and/or supporting data for other endpoints. In this discussion, each of these criteria will be considered in a stepwise fashion. The adequacy of the total database, rooted in these criteria, will also help to inform the choice of which exposure-response analytical approach(es) might be available and appropriate.

101. The process for determining adequacy begins with amassing the individual study data and judging the merits for inclusion into the analytical database, using the level of detail and type of response criteria described below. The next step is to judge the combined study data for a single endpoint based first on the criteria for the adversity and severity for the endpoint and then again for related and supporting endpoint data. The assessor should perform this analysis on the entire database amassed from the literature review. If the database is lacking and none of the three basic approaches to exposure-response analysis are tenable, then the assessor should report that data are inadequate to perform an acute inhalation assessment

and document what is known from the qualitative and limited quantitative data as potential guidance for further research directions.

Level of Detail

102. The question of adequate level of detail for response measurements for the purpose of subsequent exposure-response analysis will vary somewhat based on the endpoint under consideration. The assessor will need to make an informed judgment on response measure adequacy based on experience, precedence, and/or expert opinion. Also, see the discussion below on Type of Response Measure.

103. In general, the level of detail given in the study will guide its use in any subsequent analysis. Those studies limited to qualitative reporting of data may be limited in their usefulness to areas such as hazard identification. It is also generally true that the more quantitative information available in a study, the more useful it is for formal quantitative analysis. The decision as to where a study is in this spectrum of usefulness for qualitative or quantitative purposes should lie with the judgment and experience of the assessor.

Type of Response Measure

104. As mentioned earlier, there are three general classifications for response measures: continuous, incidence, or categorical. For continuous data, both the numeric values and units for the measure must be specified, and for BMC analysis to be used, some measure of variability has to be reported or generated. Incidence data must clearly identify the nature of the endpoint and the indicator of adversity and/or severity that places a measure into an "effect" or "no-effect" status, with either an enumeration of individuals within the exposure concentration-duration group in each status or an indication of the status for each individual subject. The criteria for inclusion of categorical data are the most restrictive. All of the criteria for incidence data also apply to categorical data, with the additional requirement that each severity category must include detailed documentation on the basis for inclusion of groups or individuals into that specific category. Lack of appropriate level of specificity for the particular type of data will result in rejection from the final analytical database.

Adversity and Severity of the Endpoint

105. This criterion is not study-specific, but will need to be assessed on all study data for a particular endpoint. The basis for determining which response level is adverse or the severity category for that response level needs to be applied rationally and consistently across all studies. This may necessitate the assessor assigning adversity levels that differ from those applied by the study(ies) author(s). Again, decision on the appropriate designation of adversity and/or severity category should be based on the available data, experience, precedence, and expert opinion.

Related or Supporting Endpoint Data

106. This criterion is most applicable to consideration of whether categorical regression or some other meta-analytical approach is viable. For categorical regression to be an option, either for exposure-response or for concentration-duration analysis, the full spectrum of severity across related effects must be part of the database. For meta-analytical approaches, multiple studies for a single endpoint must be available, with a similar study design for all included studies in order to be comparable.

2.4 Exposure-Response Analytical Approaches

107. Although each of the three analytical approaches for analyzing exposure-response relationships is presented separately here, the prudent assessor may wish to perform multiple analyses (both within each approach and between approaches) for comparative purposes. Additionally, analyses on more than one endpoint may be advisable on the basis of either providing supporting evidence for the choice of critical endpoint or to provide a ready alternative. The decision on the approach(es) to take will be based mostly on the level of detail for specific endpoint data.

2.4.1 No-Observable-Adverse-Effect Level Approach 2.

108. For the development of the Acute RfC, the NOAEL approach will be used as the default approach. It is to be used when the quantity and quality of data available are insufficient to support the use

of the BMC or categorical regression approaches. While the categorical regression approach requires multiple studies, the NOAEL approach requires a single acute inhalation study from which a sensitive adverse effect can be identified to occur at a particular concentration and duration of exposure. The NOAEL approach is suitable when the available acute inhalation toxicity data for a sensitive endpoint does not show a dose-response relationship adequate for modeling via the BMC approach. For example, a data set that shows no response at the low dose, 70% response at the middle dose, and 70% response at the high dose is not suitable for the BMC approach, but it is appropriate for the NOAEL approach.

109. As described in the Chronic RfC methodology (U.S. EPA, 1994), the NOAEL approach involves examining the existing acute toxicity database for a particular chemical to identify the critical toxic effect. The critical toxic effect is an effect pertinent to the chemical's key MOA so that if the critical effect is prevented, all other effects will also be prevented. Thus, the critical effect is a sensitive endpoint. Lethality is not considered a sensitive endpoint and is inappropriate for Acute RfC derivation using the NOAEL approach. If the critical effect is identified in animal studies, it must also be relevant to humans. Relevance to humans is assumed in the absence of information to confirm relevance. Once a good quality study that measures the occurrence of the critical toxic effect is identified, the NOAEL is chosen as the highest concentration tested at which the critical effect is not observed. A LOAEL may be used if a NOAEL cannot be identified, with modification by an appropriate UF. The NOAEL or LOAEL then serves as the POD to derive the Acute RfC by the subsequent application of dosimetric adjustments and UFs as necessary to derive a concentration protective of sensitive human subpopulations. Any POD based on a NOAEL/LOAEL or BMC will be for a specified duration such that duration extrapolation will need to be undertaken for estimation of other pertinent durations.

2.4.2 Benchmark Concentration

110. The Use of the Benchmark Dose Approach in Health Risk Assessment (U.S. EPA, 1995) was published by the Agency to identify the methodological choices and issues in using these methods to replace the NOAEL approach, but guidance on the use of BMD/C methods has yet to be finalized. The guidance on the use of BMC in this document can be viewed as preliminary and should be adjusted, if necessary, to be consistent with Agency guidance when it is available. To ease the implementation of BMC methods, the Agency has developed Benchmark Dose Software, which can be obtained without cost at http://cfpub1.epa.gov/ncea/cfm/bnchmrk/versions. cfm?ActType=default.

111. The BMC will be used as the basis for derivation of the Acute RfC when good quality quantitative information is available from at least one study when multiple studies (for a number of exposure durations) required by the categorical regression approach are unavailable or are otherwise unsuitable. As with the NOAEL approach, only a single good quality inhalation study is required for BMC analysis, but the dose-response data must show a steadily increasing (monotonic) response with increasing exposure concentration.

112. The BMCL is a lower statistical confidence limit on the dose corresponding to a specifie level of risk, the Benchmark Response (BMR) (see Figure 2-4). Thus, before calculating a BMCL, the BMR must first be specified. Several considerations may influence the selection of a BMR. The first consideration is that, when used for determining the Acute RfC, the BMCL is used as a POD like the NOAEL. This suggests that the BMR should be selected near the low end of the range of increased risks or observable data that can be detected in a bioassay of typical size. Comparison of the BMCL with the NOAEL for a large number of developmental toxicity data sets indicated a BMR in the range of 5 to 10% resulted in a BMCL that was, on average, similar to the NOAEL (Allen et al., 1994a,b; Faustman et al., 1994). Although not applicable to developing an Acute RfC, examples of inhalation studies for both low level chronic exposures (Gift, 1996) and short-term lethality (Fowles et al., 1999) show that a BMR in the range of 5 to 10% yields BMCLs similar to NOAELs. For dichotomous data, a single probability of effect may eventually be selected by the Agency as the basis of the BMCL. This approach is only reasonable if the dichotomous endpoints to which the single probability of effect would be applied are all of similar toxicologic adversity. However, definitive application of a single probability of effect to the BMC approach awaits systematic investigation of data for various target endpoints in relation to oral and inhalation exposures. In the interim, the 10% response has been adopted as the default BMR for dichotomous data.

113. Several approaches can be used to determine the BMCL for continuous data. One approach is to define a magnitude of change (i.e., the BMR) considered to be an adverse effect and then use the BMCL predicted for this BMR as the POD. Another approach is to convert continuous data to dichotomous data by using the defined magnitude of change to mark the upper limit of the no-effect response. Then, all individual responses equal to and below that limit are counted as no-effect responses, and all individual responses above that limit are counted as adverse responses. A third approach is a statistical method that calculates quantal responses from continuous data (Crump, 1995). The Agency is also developing and evaluating statistical models that convert continuous data to dichotomous data. Final models will be implemented in updates of the Benchmark Dose Software.

114. For dichotomous data, it is recommended to use "extra risk" as the default procedure for the manner in which the BMR for dichotomous data is calculated.

$$ExtraRisk = \frac{P(d) - P(0)}{1 - P(0)}$$

where, *P(d)* is the probability of response at dose *d*, and *P*(0) is the probability of response at dose 0 (i.e., background). In the case where background *P*(0) is zero, the response would be equal to the absolute value of the designated response (e.g.,10%). When background values are present, the designated response would have to be increased to offset this value such that the change would be in the population that is not already affected at the designated response value (i.e., the remaining population at risk, 1 - *P*(0)).

115. All continuous effects require an accompanying biological rationale as to the level that is adverse. The application of the benchmark approach to continuous data therefore requires that the BMR be set specifically for each endpoint and expression of results. Because of this difference in data and modeling attributes, it is not unreasonable to use different approaches for continuous and dichotomous data.

116. BMR choices for continuous models include Relative Deviation, Absolute Deviation, Standard Deviation, and Point. *Relative Deviation* is calculated as the difference (plus or minus, depending on the measured effect) between (1) the product of the estimated background level for the measured parameter multiplied by the chosen BMR Factor (e.g., 10%) and (2) the estimated background level. In other words, Relative Deviation is the response rate above/below the background level that is judged to be adverse. *Absolute Deviation* is more simply the product of the background level multiplied by the BMR Factor (i.e., no correction for background level). *Standard Deviation* is calculated as the difference between the product of the BMR Factor (e.g., 1 or 2) multiplied by the calculated standard deviation for controls, and the mean for the control data. *Point* is most simply the level defined by the BMR Factor as being adverse; in other words, a Point BMR is a strictly defined level that does not take into account statistical variability either within the control or the exposed groups.

117. In general, BMC analysis makes maximal use of the quantitative data available from an individual study, regardless of whether it is continuous or dichotomous. This attribute of BMC has to be kept in mind when evaluating the various approaches to be employed for exposure-response analysis. With categorical regression, for example, a significant loss of quantitative response information from a study can result when detailed continuous information is converted to ordinal categorical designations.

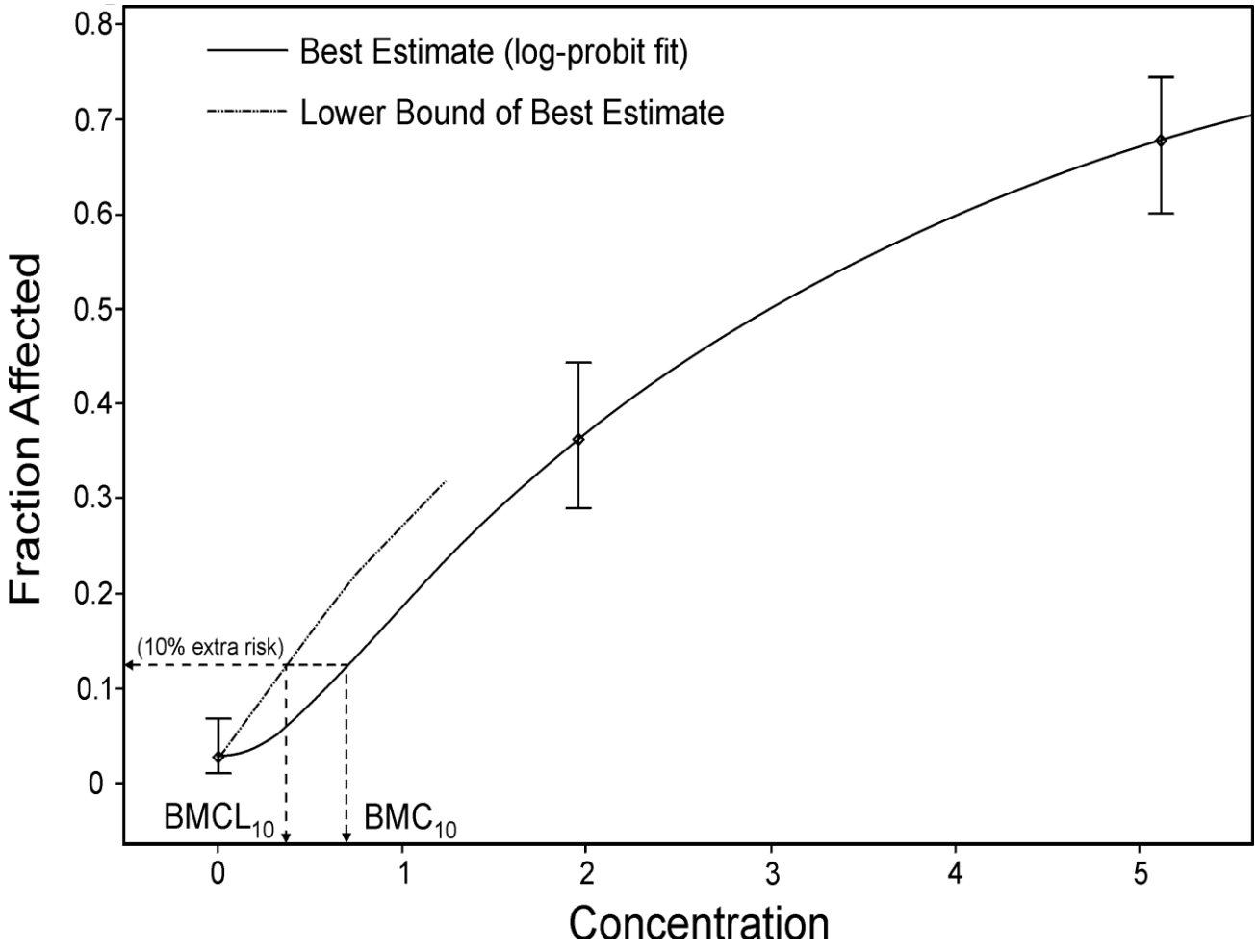

Figure 2-4. Example benchmark concentration analysis using log-probit model from BenchmarkDose (U.S. EPA, 2000c). BMC10 is the concentration associated with a BMR of 10% (extra risk). BMCL10 is the 95% lower confidence limit of the BMC10. (◊) data with 95% confidence.

Standard Procedures

118. For Acute RfC development, the BMC and the BMCL should be calculated for each effect, showing sensitive effects in the acute duration range. Estimates from several different BMC models should be calculated, and the results should include both graphical and tabular display of the data and model estimates as well as goodness-of-fit tests. Based on this analysis, a preferred BMCL should be selected based on a documented rationale that should include a description of endpoint, model choice, and any additional manipulation of data. Criteria for model choice in BMC analysis must be regarded as a work in progress; simple set procedures holding for all situations are not likely to be developed. In general, however, such factors as AIC values, chi-square residuals, consistency in output among models and visual judgment all need to be called into consideration in making the model choice.

119. The BMCL then serves as the POD to derive the Acute RfC by the subsequent application of dosimetric adjustments and UFs as necessary to derive a concentration that is protective of sensitive human subpopulations. If the chosen study uses an exposure duration other than the duration of interest for Acute RfC derivation, a duration adjustment must also be made using the duration extrapolation analysis utilized in the assessment.

120. Little attempt has been made to define the minimum data set required to perform a BMC calculation. U.S. EPA (1995) recommends that the minimal study have at least two groups with responses above controls. For the purpose of the Acute RfC, the minimum data set recommended for benchmark

modeling consists of at least two dose levels with greater than zero but less than maximal response and with at least three dose levels overall.

2.4.3 Categorical Regression

121. The use of categorical regression is an approach suitable for purposes of dose-response analysis and, more importantly for acute assessments, for estimation of the concentration-duration relationship. Categorical regression becomes an option for these purposes when there are multiple acute inhalation studies for a variety of exposure durations for the chemical of interest. Good quality studies that report exposure concentration, duration, and effect data can be used. The categorical regression approach can accommodate several types of response data (i.e., descriptive data, continuous data, dichotomous data, and a variety of toxic endpoints and species as well as gender) as long as the responses can be classified into severity categories. The use of a number of studies at various exposure durations allows effect severity to be predicted across both exposure duration and concentration continua.

122. Categorical regression uses response data, classified by severity category, and the associated exposure data (concentration and duration) to estimate the *probability*, or likelihood, that an effect of a certain severity will occur at various concentrations and durations of an inhaled chemical (i.e., to estimate the proportion of a new group of animals that will experience the effect at a given concentration and duration combination). Classifying response data by severity allows the technique to be applied to many studies and to any number of species. For example, many different descriptive or quantitative measurements made in a variety of species may be judged as a "mild adverse effect."

123. The software developed for this purpose, CatReg (http://www.epa.gov/ncea/catreg.htm), uses general logistic regression methods to develop models of the relationship between severity of response, exposure concentration, and exposure duration. With the inputs of exposure concentration and duration for each response (categorized by severity level), the models estimate parameters relating these inputs to a probability regarding response in each severity category. Once data is entered, CatReg has the capability to estimate these parameters from any aspect of the data as stipulated by the assessor such that certain aspects of the database are displayed (e.g., the concentration-duration relationships for a certain species or for all species combined). Further, it is possible with CatReg to specify and examine different subsets of the data (e.g., two different species) and determine statistically whether outputs such as the concentration-time confidence bounds on the central regression estimate. Other curves and bounding estimates can relationships are the same or different from one another. Additional details are available from the CatReg User's Manual (U.S. EPA, 2000d).124. Figure 2-5[1] is a representative concentration-duration plot from a CatReg analysis. The downward sloping solid curve is the regression line generated by CatReg for the 10% probability of occurrence of an effect of "adverse" severity. The flanking dashed curves are the 95% confidence bounds on the central regression estimate. Other curves and bounding estimates can be generated for different probability estimates and severity categories. The curves are generated from input data on exposure duration, exposure concentrations, and effect severity. As described elsewhere, these data can be for a variety of endpoints (with the requirements that they can be categorized as to severity). Alternatively, the data can be stratified (analyzed separately) by endpoint or any other distinguishing feature of the database (e.g., species) such that the intercept, concentration and/or time parameters of the CatReg model are optimized separately for the given endpoint/feature.

125. The curves are relatively distant from the "adverse" data they are estimating as they are not the actual maximum likelihood estimate, but rather the lower 10% probability of observing an "adverse" effect. These data-driven curves define the concentration-duration relationship for this particular severity

[1] The terminology used in this document to describe CatReg plot results supersedes terminology used in previous documents and reflects important changes to the way the current R-version of CatReg calculates and reports probability estimates. The previous, SPlus version of CatReg reported the time-dependent central tendency for the probability of an X% response and referred to it as the EC-T_X. To be consistent with other EPA dose-response methods (e.g., BMD methods), the current R-version of CatReg calculates and reports the central tendency and 95% one-sided (90% two-sided) lower confidence limit on the extra risk of an X% response, and refers to them as the ERC-T_X and LERC-T_X, respectively

effect. The concentration and corresponding duration estimated to give this 10% probability of observing this severity effect may be read directly from these curves.

Minimum Data Requirements

126. The form of categorical regression used by the Agency, CatReg, uses duration as an independent variable and requires data for more than one duration to generate concentration-duration plots. Limited study of the minimum data requirements for this method has been performed. A provisional minimum database requirement is for the studies combined for analysis to have data for at least two durations separated by a minimum of 3 hours and at least no-observable adverse effect (NOAE) and adverse effect (AE) severity categories at each of those durations. Since the Acute RfC methodology focuses on identifying toxicity benchmarks for sensitive effects, the focus of the categorical regression approach is on mild adverse responses. Until more analysis is performed in this area, it is recommended that a balance be struck between reliance placed on information for more severe endpoints (e.g., lethality) and for mild adverse effects.

Standard Procedures

127. For the categorical regression approach, dosimetric adjustments must be applied to the data prior to the categorical regression analysis. To be consistent with benchmark dose methods, the 95% lower confidence limit of the effective concentration-time for a 10% probability (LERC-T_{10}) of effects at the designated severity level (typically not-adverse to mild-adverse) is recommended as the POD (actually a "line" of departure) for Acute RfC development. The rationale for assigning severity categories for each study should be completely documented. Documentation of categorical regression results should include model options, goodness-of-fit parameters, ERC-T_{10} and LERC-T_{10} estimates for durations of interest (typically 1-, 4-, 8- and 24-h), and a graphical display of the data and regression lines. Based on analyses varying model options and data sets, a preferred model should be selected based on a documented rationale that should include a description of model choices and any additional manipulation of data. To derive the Acute RfC, the PODs derived from the concentration-duration line are adjusted by the application of UFs as necessary to derive a concentration that is protective of sensitive human subpopulations.

2.5 Duration Extrapolation Determination

128. The concepts for performing duration extrapolations were introduced in Section 2.3.2. For the purposes of performing an acute inhalation assessment, the steps for this aspect of the process of developing an Acute RfC are illustrated in Figure 2-6. Duration extrapolation is not necessary for a POD calculated by categorical regression.

129. As shown in Figure 2-6, if adequate data are available it may be possible to derive an endpoint-specific duration slope factor (value of *n* from the $C^n \times T$ equation). The example assessment for phosgene is a case in point where sufficient data on both endpoint and durations are available, allowing for a chemical- and endpoint-specific value of *n*. The work of ten Berge et al. (1986) provides the method for deriving a value of *n* based on dichotomous data, and software has been developed (ten Berge, 2000) to allow calculation of this value.

130. Another chemical-specific option for a value of n may be to use a previously calculated value for lethality or to derive one from reported lethality data using the ten Berge (2000) software. As has been discussed earlier in Section 2.3.2, however, this option may have considerable liabilities. Such a value of n is likely derived from high-level exposure studies in which homeostatic defense mechanisms are overwhelmed, a situation where the target organ(s) may differ or may not be discernable from those of lower-exposure studies in which homeostatic mechanisms are operating and the chemical is being handled by these systems.

131. Use of lethality slope factors, however, are tenable only if the MOA for lethality is similar or may be linked to the MOA for the sensitive endpoint used as the Acute RfC POD. Examples of calculated values of *n* for 20 chemicals based on lethality data are provided in ten Berge et al. (1986).

132. The acute assessment of HCCPD is an example of the use of this option. A value of *n* was developed from available lethality data of different concentration-durations combinations and used to

extrapolate for occurrence of a less-than-lethal endpoint, pulmonary toxicity. In the case of HCCPD, however, information was available indicating that the target organ (lung) at the high-level exposure studies was the same as in the lower-exposure studies.

133. The default approach for a value of *n*, when all other options are unavailable, is to use values of $n = 3$ for durations shorter than the observed POD(s) and $n = 1$ for longer durations. As can be judged from Figure 2-3, values of *n* of 3 or greater have little slope and this property restricts extrapolating to higher exposure concentrations where data may not be available for durations shorter than observed in the key study(ies). Conversely, a value of *n* equal to 1 applied to longer durations imparts a pronounced downward slope such that extrapolation results in proportionately smaller concentrations. This is also in keeping with the National Research Council's recommendations (National Research Council, 1993) that are currently used by the NAC/AEGL for developing AEGL values and are reflected in their current AEGL Standing Operating Procedures (SOPs) (National Research Council, 2001).

2.6 Acute Rfc Derivation

134. Following the use of one or more of the exposure-response analytical approaches described in Section 2.4, an appropriate POD will be selected. The POD is then subjected to additional adjustments for dosimetry and duration as necessary, and finally relevant UFs are applied to arrive at the final Acute RfC values.

2.6.1 Determination of the Point of Departure

135. The approach proposed for the health assessment of acute inhalation exposure is the development of an estimate of a predetermined effect level (POD, e.g., $BMCL_{10}$, or ERC-T_{10}) based on the best available exposure-response model and the application of UFs for various extrapolations and data gaps. The exposure-response model used to determine the POD would be determined largely by the availability of data. As suggested and demonstrated in the preceding sections, results from the categorical regression approach, the BMC approach, as well as the NOAEL approach should all be considered as the potential POD. Each approach has certain strengths and weaknesses and, depending on the data that are available, one or more could be applicable. In general, a preference would be given to models that use more exposure-response information (e.g., categorical regression and BMC), but this is a decision based on the nature of the studies, amount of data applicable to the models, the agreement between the results of the models, and the size of the confidence bounds for the applicable models. When data permit, a comparative analysis among these approaches may be undertaken and is recommended to aid in the quantitative analysis of uncertainty.

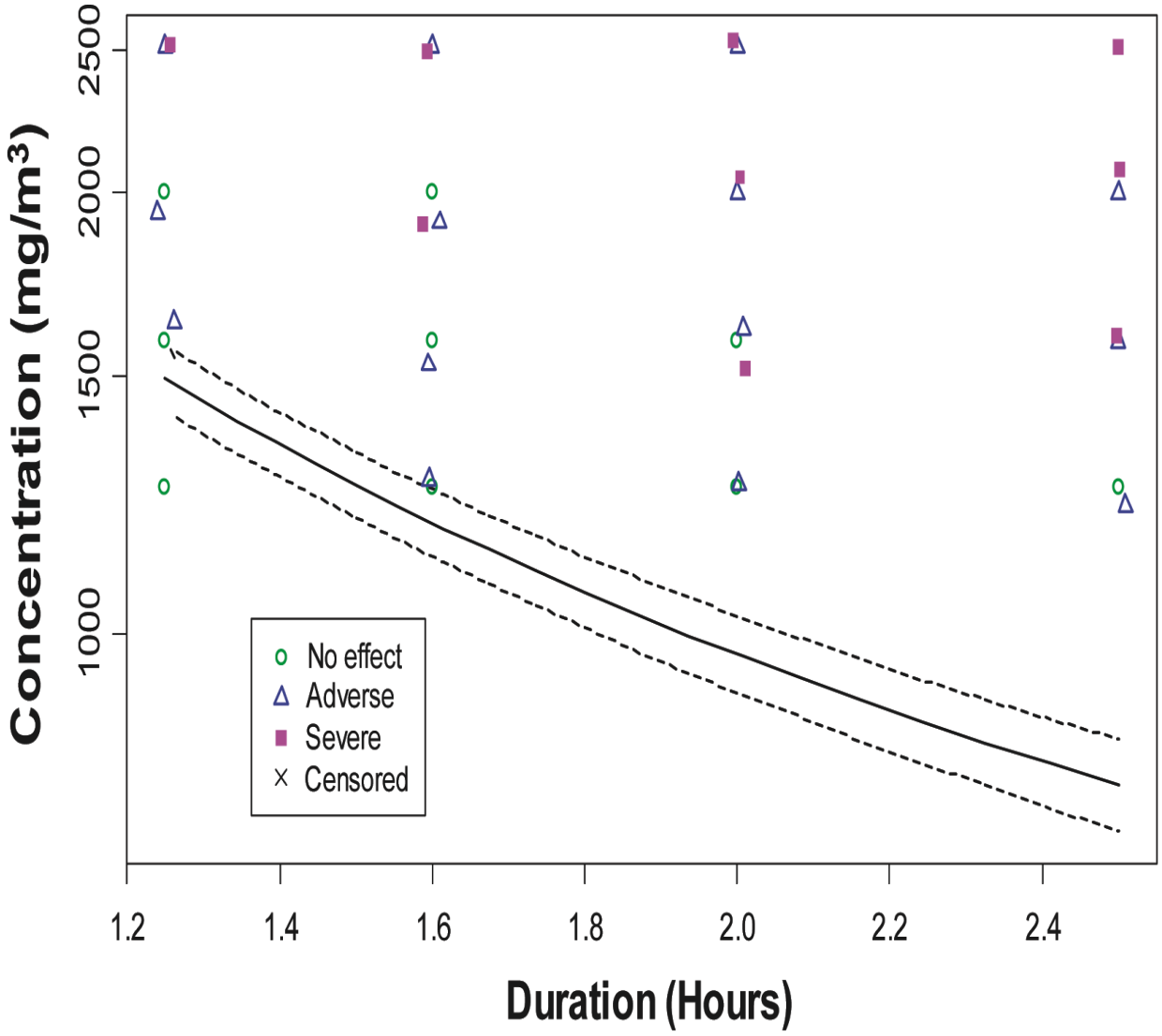

Figure 2-5. A CatReg concentration-duration plot for a specified severity category. Symbols indicate simulated toxicity data of different severities (from "No effect" to "Severe"). The solid line is the estimated for the 10% probability of occurrence of an effect of "adverse" severity, the ERC-T10. The dashed lines are the 90% two-sided (95% one-sided) confidence bounds for the ERC-T10, with the lower bound being designated the LERC-T10.

136. For the BMC approach, the critical decision is the designation of a specific adverse effect (or risk) level. The BMCL, the POD for the BMC approach, is the 95% lower confidence bound on the concentration corresponding to the BMR. The BMCL is used like the NOAEL and implies that the effect (or risk) level in the BMC approach is close to the onset of an adverse effect. Presuming it to be a minimum adverse effect, this interpretation is consistent with the interpretation of the onset of adversity for categorical regression. Because both methods adopt the same approach for analysis of continuous data, the designation of an adverse effect level based on statistical and biological considerations, the BMC and categorical regression approaches are consistent in their use of continuous data.

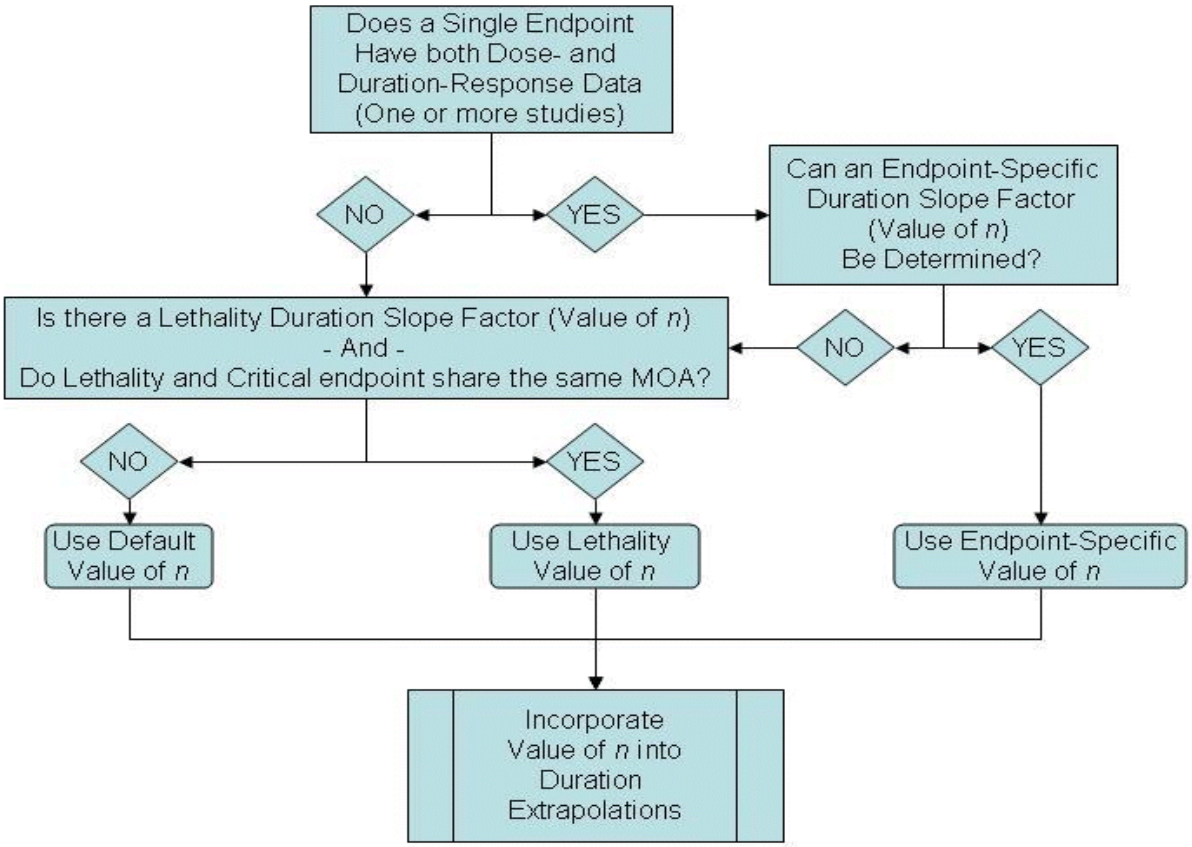

Figure 2-6. Decision tree for determining duration slope factor (value of n).

137. That the BMCL for dichotomous data is based on a percent response determined without consideration of severity (e.g., 10%) could be regarded as an inconsistency if the defined limit for adversity used in categorical regression is different from the BMR (i.e., greater or less than 10%). This is likely to be rare, however, because the 10% incidence likely to be adopted as a BMR would most likely be for effects judged mild to moderate in severity. The ERC-T_{10} and LERC-T_{10} derived from the categorical regression analysis will be interpreted as equivalent to the BMC for a 10% incidence of a dichotomous effect or an effect equal to the specified effect level for continuous data, despite the possibility of inconsistency discussed above. Likewise, the 95% lower confidence bound on the ERC-T_{10} from categorical regression (i.e., LERC-T_{10}) will be interpreted in the same way as the $BMCL_{10}$ and the NOAEL and is thus the POD for the categorical regression approach for dichotomous data.

138. The selection of the POD to be used as the basis for the health assessment will result from a review of the candidate POD values. These candidate values may include the results from a categorical analysis that is determined to produce the best description of the available data, the BMC results on individual data sets, and the NOAELs.

2.6.2 Dosimetry Adjustments: Calculation of the Human Equivalent Concentration(HEC) for Acute Exposures.

139. The approach taken in this document is to recommend a hierarchy of procedures (from default to optimal, based on data availability) for performing dosimetry adjustments on study results from acute inhalation exposures in laboratory animals to derive exposure concentrations that are relevant to humans.

This adjustment to a Human Equivalent Concentration (HEC) can be determined for all exposures to inhaled agents, both gases and particles, through the use of available valid models.

140. Based upon the rationale discussed more fully below and on the already existing discussion presented in the (draft) ARE documentation (U.S. EPA, 2000a), the recommended default procedure for determining the HEC for all acute-duration gas exposure in laboratory is application of a dosimetric adjustment factor (DAF) of 1, as indicated in Equation 2-1:

$$\text{Exposure Concentration in animals (mg/m3)} \times 1 = \text{HEC} \qquad (2\text{-}1)$$

141. Aspects of the U.S. EPA methodology for chronic inhalation dosimetry (U.S. EPA, 1994a) are not directly applicable to acute scenarios due to certain temporal aspects and uncertainty regarding internal dose. Nevertheless, many of the underlying concepts and most of the terminology are harmonious with the acute inhalation dosimetry recommended in this section. The application of these relevant concepts to acute dosimetry is the focus of this discussion. It should also be noted that the Chronic RfC methodology is being revised and that the effort to develop inhalation risk assessment methods for less-than-lifetime durations is being coordinated with those revisions.

Dosimetry in Chronic Exposures

142. To accommodate species differences in inhaled dose, dosimetric adjustments are made to exposure concentrations used in experimental animal studies to yield an HEC. The intention of dosimetric adjustment is to provide an estimate of internal dose at the target tissue (or area of effect) in the test species produced by a given external concentration; the corresponding external concentration for humans that produces that same internal dose is the HEC.

143. The general equation for the calculation of an HEC as developed and presented in U.S. EPA (1994a) is through application of a DAF to the exposure concentration of an animal inhalation exposure, as shown below in Equation 2-2:

$$\text{Exposure Concentration in animals (mg/m}^3\text{)} \times \text{DAF} = \text{HEC} \qquad (2\text{-}2)$$

Defined procedures are available for estimating HECs under a variety of conditions for both gases and particles and for a wide range of data availability (U.S. Environmental Protection Agency, 1994a). Procedures are included for the entire respiratory tract, for any of its regions, or for the whole body (referred to as systemic or extrarespiratory) in response to a reactive/water soluble gas, an insoluble/nonreactive gas, a gas of intermediate reactivity/solubility, and particles. The procedures are intended to be applied in a hierarchy as indicated in Table 2-3, ranging from optimal to default procedures with the optimal application being ideal information integrated into an ideal interpretative structure. An example of an optimized instance would be where sufficient data relating to dosimetry are available and integrated into a useful PBPK model to estimate an HEC from any given exposure of any laboratory species. To accommodate cases most often available (i.e., where dosimetric information is default procedures using various surrogate procedures and assumptions are also available (U.S. Environmental Protection Agency, 1994a).marginal)

The intent of dosimetry adjustment in this document and in U.S. EPA (1994a) is for interspecies adjustment of an externally applied inhalation exposure to achieve the same internal concentration, the ultimate and most appropriate determinant of risk. As pointed out above, the procedures for accomplishing this adjustment are intended for chronic exposure scenarios (U.S. Environmental Protection Agency, 1994a). A more in-depth examination of these procedures, however, indicates a harmonious manner in which these procedures may be applied to the acute exposures scenarios described in this document.

144. In exposing humans and laboratory animals to systemically distributed gases (i.e., gases that are delivered to the target tissue otherwise unaltered), experimental evidence indicates that the values of the partition coefficients ($H_{b/g}$) are identical in humans and laboratory animals. This leads to the logical prediction that, at steady state, the systemic concentration of the gas would be the same or be very similar for both species.

145. In considering this example, it would be apparent and logical that species differences would likely exist prior to achieving steady-state. For the example of an inhaled unaltered gas, a principal influence of determining when steady-state is achieved is a time-related process, the rate at which the gas is delivered to the air:gas interface (i.e., the alveolar ventilation rate). Alveolar ventilation rates scale according to the body weight raised to the 3/4 power – $BW^{3/4}$(Guyton, 1947; Vocci and Farber, 1988; Travis and Bowers, 1991). This scaling relationship indicates that smaller species will (and in fact do) have alveolar ventilation rates proportional to body weight that are greater than the larger animal. For example, an alveolar ventilation rate of 4200 mL/min for a 70-kg human yields a ratio of 60 mL/kg, whereas the $BW^{3/4}$-scaled alveolar ventilation rate for a 0.3-kg rat of 70 mL/min yields a ratio of 230 mL/kg, a value nearly 4-fold higher than what is seen in humans.

146. A consequence of this relative difference in alveolar ventilation rates between species would be the more rapid introduction of inhaled agent into the rat relative to the human, thereby resulting in a more rapid and steep rise to an internal steady-state concentration in the rat. A more rapid and steeper rise to steady-state with the rat would mean that at any given time prior o achieving steady-state, the internal concentration in the rat will be higher than in the human for the same external concentration. As these conditions would occur during the initial phases of an exposure, they would have special application to acute exposure scenarios.

Table 2-3. Hierarchy of Model Structures for Calculation of a Dosimetric Adjustment Factor (DAF) for Interspecies Extrapolation (adapted from the *RfC Methods* document).

Optimal model structure:
(a) Uses description of all significant mechanistic determinants of chemical disposition, toxicant-target interaction, and tissue response
(b) Uses chemical-specific and species-specific parameters
(c) Dose metric described at level of detail commensurate to data available
Default model structure:
(a) Uses limited or default description of mechanistic determinants of chemical disposition, toxicant-target interaction, and tissue response
(b) Uses categorical or default values for chemical and species parameters

147. The differences actually existing between laboratory animals and humans at these early exposure times could theoretically be addressed by adjusting the inhaled external concentration, i.e., to offset the lower dose-rate in humans by breathing a higher external concentration. For those gases that are distributed and have manifest toxic effects systemically, available data shows that the absolute values for animals $(H_{b/g})_A$ is greater than human $(H_{b/g})_H$ for nearly all known cases (Gargas et al., 1989; Jepson et al., 1994). As this would also mean that factors greater than 1 would be applied to experimental concentrations, U.S. EPA (1994a) directs a maximum value of 1 be used such that the DAF=1.

148. Rather than attempt any such adjustment, it would be reasonable to just assume that the corresponding human dose rate would be at least equal to the animal dose rate. When applied to the external exposure airborne concentration, this practice would assume no differences in dose rates to exist between laboratory animals and humans at the same external concentration of a given agent.

149. The foregoing arguments may also be considered to apply to inhaled gases manifesting effects in portal-of-entry tissues (respiratory tract), as the interspecies relationship of surface area is also related to a function of body weight (U.S. EPA, 1992).

150. Therefore, certain aspects of the default procedures used in the chronic dosimetry document procedures apply to acute exposures to gases, whereas other aspects do not. In recognition of the interspecies relationship described above with gases regarding temporal aspects of internal dose, of the uncertainty inherent in these procedures, and of the original intent of use for chronic scenarios, the default procedures for chronic exposures of interspecies gas dosimetry are not considered directly applicable in this Preliminary Methodology Document on acute exposures.

151. As noted above in Equation 2-1, the recommended default adjustment of an animal exposure to an HEC for all gases is 1. A DAF of 1 is also directed in the case where either the animal or human $H_{b/g}$ is unknown; therefore, this recommendation is consistent and in harmony with the *RfC Methods* document (U.S. EPA, 1994).

152. Also, results from advanced modeling procedures have found actual values for the adjustment factor between rats and humans to approximate unity in the cases of methyl methacrylate and vinyl acetate (see review by Andersen et al., 2002).

The DAF for Acute Particle Exposures

153. Although acute duration exposures were not considered in the *RfC Methods* document (U.S. EPA, 1994), most procedures and models available for particle dosimetry may be considered to have at least some application to acute exposure scenarios as the underlying and supporting information (e.g., upper airway fractional deposition patterns for particles are based on short-term exposures that fit within this document's definition of acute).

154. Consequently, for calculation of the DAF for an acute exposure to particles involving rats, consideration is recommended of the most recent version of the Multiple Pass Particle Dosimetry Model (Anjilvel and Asgharian, 1995) and other articles on the use and adaptation of this model (Jarabek et al., 2005; Cassee et al., 2002).

2.6.3 Duration Extrapolations

155. Since categorical regression analysis can predict an effective concentration for a duration of interest even if there are no data for that exposure duration, no duration extrapolation is necessary. Additionally, where appropriate, the slope of the CatReg regression line may be applied to define the concentration-duration relationship with a single duration POD, either a NOAEL or BMCL.

156. However, when Acute RfCs are derived from a single duration estimate (i.e., the NOAEL or the BMCL), there may be a need to extrapolate to other acute durations in order to estimate risks at additional exposure durations of interest. No UF for duration adjustment will be used. The following general discussion provides information relevant to duration extrapolation, as well as interpolation between two or more single-duration Acute RfCs.

157. For a chemical for which there is sufficient pharmacokinetic information available, use of a PBPK model is the preferred method for duration extrapolation. Once the proper dose metric is determined, the PBPK model may be used to calculate the dose level that is associated with the critical effect. The PBPK model can then be used to estimate the effective dose associated with any concentration and duration of interest.

158. In the absence of sufficient pharmacokinetic information, conservative default adjustments are recommended. A reasonable approach is to assume a relationship in the form $C^n \times T = k$ with $n = 1$ to

extrapolate from the longest duration model result to longer durations of interest and to use $n = 3$ to extrapolate from the shortest duration model result to shorter durations of interest. This is likely to be health protective because evidence available on a number of systemically acting chemicals show that their values are prone to fall in the range of $0.8 < n < 3.5$ (ten Berge et al., 1986).

159. If adequate data are not available for the critical endpoint but do exist for some other endpoint (usually lethality) such that a slope factor (value of *n*) can be derived, and the MOA is assumed to be similar, then that alternate *n* value may be used with the critical effect POD. In ten Berge et al. (1986), *n* values were determined for 20 chemicals along with a discussion of the method used to determine those values.

160. A worst case alternative for extrapolation to shorter durations is to assume a horizontal line from the shortest duration modeling result to the duration of interest (i.e., "flat-lining"). This assumes a strictly concentration-related effect, and it is recognized that this approach could be extremely health protective at very short durations but avoids extrapolating to higher and higher concentrations in the absence of supporting data. However, because it is clear that some agents do show concentration dependence with very little effect of duration, and because the typical upward slope of the response curve at short time periods would extrapolate values to higher and higher concentrations, it may be prudent to assume this pattern if there is no evidence of a $C^n \times T$ type of relationship (e.g., for irritation effects that are usually concentration dependent).

161. A possible alternate approach for extrapolation to durations longer than the longest experimental result includes use of studies with from two to several days of exposure to interpolate to the duration of interest.

162. Interpolation might also be necessary if the best available approach resulted in more than one single duration estimate, but concentration-duration-response modeling was not possible because of inadequate data. In this case, the approach will be to interpolate linearly on a log-log scale between the lower bounds on the estimates at the available durations to arrive at the Acute RfC for the duration of interest.

2.6.4 Application of Uncertainty Factors

163. As with the approach to Chronic RfC development, UFs should be used to address areas of data gaps that cannot be accounted for by data or modeling analysis. The UFs that are possibly relevant in the context of acute health assessment are typically factors of 10 for the areas discussed in this section. In cases when a full UF of 10 is not required, a partial UF of $10^{1/2}$, or 3, will be applied. Since the partial UF of 3 represents a geometric half of the full 10 (rounded to one significant figure), two factors of 3 would combine to give a factor of 10.

LOAEL to NOAEL Uncertainty Factor

164. Exposure-response modeling approaches, such as the BMC and categorical regression approaches, will identify a 95% lower bound on the concentration predicted by the best available model. Because this value is assumed to be equivalent to a NOAEL, no UF for LOAEL to NOAEL is required. If data are inadequate for mathematical modeling, the NOAEL approach will be used to derive the Acute RfC. However, in some cases only a LOAEL is available. A UF of 10 is recommended as a default for LOAEL to NOAEL extrapolation. Data regarding the steepness of the dose-response curve may be used to depart from the suggested default.

Interspecies Uncertainty Factor

165. When no adequate human data are available, a UF for interspecies variability will be applied to the result of the best available exposure-response assessment, regardless of whether it is a categorical regression analysis, a BMC analysis, or a LOAEL or NOAEL at a single duration. Current U.S. EPA practice divides the traditional default value of 10 for the interspecies extrapolation into pharmacokinetic and pharmacodynamic components, with a partial UF of $10^{1/2}$ (rounded to 3) for each. The dosimetry adjustments recommended in Section 2.6.2 account for the pharmacokinetic component of interspecies uncertainty and obviate the need for $10^{1/2}$ of the default value of 10. Thus, when dosimetry adjustments are

used, a factor of $10^{1/2}$, to account for pharmacodynamic differences, is recommended. If any human data on sensitive endpoints are available, attempts will be made to use them directly, in which case this UF is not needed.

Intraspecies Uncertainty Factor

166. Information on sensitive human populations is extremely rare. Sensitive human subpopulations may include the very young (infants and children), the elderly, or those individuals with a chronic disease condition (e.g., asthma, chronic obstructive lung diseases). Special consideration should be given to the relative sensitivity of children and adults. Current Agency information and/or policies regarding the protection of children should be incorporated as appropriate into Acute RfC assessments. A default UF of 10 is recommended when information on sensitive subpopulations is inadequate. An Acute RfC derived from sensitive subpopulations may motivate reduction of this UF to a value lower than 10.

Table 2-4. Determination of Database Adequacy

Database Characteristic	Minimal	Preferred
Concentration Data	NOAEL	Multiple exposure concentrations with at least 2 at or above an effect level but below maximal response
Duration	Duration noted (some studies lack this information)	Multiple durations (e.g., 1-h, 4-h, 8-h), for multiple exposure concentrations
Response Data		
Incidence	Status by group	Data on status of each individual*
Categorical	Category by group	Category designation for each individual*
Continuous	Means by group	Measure for each individual*

*Individual refers to an experimental unit, which can be an individual animal or litter in developmental studies.

Database Uncertainty Factor

167. The Acute RfC, by the definition given in this Document, is intended to cover only short-term exposures that would likely not be inclusive of any specific life-stage already accommodated by the intrahuman variability factor. In the instance of other data indicating a potential for an effect that may have relevance at short duration of exposure (e.g., developmental effects), it may be prudent to evoke at least a partial UF for missing data of acute exposure duration. Any further consideration for database uncertainties may be informed by referring to other toxicological data for the agent (e.g., results from subchronic or chronic studies).

168. Table 2-4 provides some useful considerations when assessing the quality of the database, as well as for assessing individual studies. The value for any partial UF should be guided by precedents to capture the rationale already extant in the risk assessment community. Thus, factors for missing aspects of the database are proposed to be values of either 3 or 10.

2.7 Final Considerations

169. The final product from this process is a set of Acute RfC values for specified duration points. The default durations are 1-, 4-, 8-, and 24-h. There may be unforeseen needs, however, for other durations and the information used to develop values for the default durations may be sufficient to also derive values for other time points. Before doing so, the assessor is cautioned to not extrapolate too far from the observed data. For example, the NAC/AEGL SOPs (National Research Council, 2001) specify that AEGL values for 10-min cannot be extrapolated from observations of 4-h or longer, and that the 30-min value should be adopted for the 10-min duration (i.e., flat-lining).

170. An integral part of applying an Acute RfC will be an understanding of the relationship of the derived values to other acute reference values. As mentioned in Chapter 1 of this document, a number of other acute reference values have been devised for other applications. Although how the Acute RfC compares with those other acute values should not affect the process, an acknowledgment and discussion of correspondence or differences between values will likely be valuable to anyone attempting to choose an appropriate reference value for a specific purpose. Tables and/or graphs may be useful for simple comparisons with accompanying text to provide more details and should be considered as an appendix to the assessment document.

3. SUMMARY OF EXAMPLE ACUTE RfC ASSESSMENTS

171. This section of the Preliminary Methodology Document provides a brief explanation of how the steps and procedures described in Section 2 have been used in developing the example Acute RfC assessments for four chemicals: ethylene oxide (EtO), hexachlorocyclopentadiene (HCCPD), hydrogen sulfide (H_2S), and phosgene. The full IRIS Toxicological Reviews for each of these example assessments are available upon request. Some of the elements from each of those assessments have been repeated here to illustrate particular points; however, the intent was to minimize duplication, and the reader is directed to the Toxicological Reviews for more details on individual assessments.

172. Each of the discussions for the four example acute assessments includes at least the following six elements: (1) identification of the critical endpoint(s); (2) discussion of the MOA; (3) the approach used in the dose/exposure-response analysis; (4) the approach used in the analysis of the duration relationship: (5) description of the database and identification of data gaps; and (6) confidence in the assessment, including individual elements of the assessment.

3.1 Ethylene Oxide (Eto)

173. The exposure-response array for EtO, depicted in Figure 3-1, shows the entire dose range included in the study (with the exception of nonexposed controls). The upper and lower limits on the bars represent the high and low concentrations, respectively. If a NOAEL and/or LOAEL were identified in the study, they are represented by a triangle or diamond shape, respectively. In many cases, only a single concentration is shown. The results are arranged by duration, as defined across the upper horizontal axis, with exposure durations ranging from less than 10 minutes to 6 hours. Within each duration category the results are secondarily ordered on the severity of the effect (e.g., lethal effects are all at the right side of each duration category, if there are any, and are delineated by shaded boxes). Finally, the results are ordered by the lowest to highest "low" concentration within the severity category.

174. The endpoint chosen for the acute assessment of ethylene oxide (EtO) was neurological effects, notably, the presence of effects in both of the Functional Operational Battery (FOB) measures "low response" and "approach response - no reaction" in male rats, as noted in the study of Mandella (1997). This study is an unpublished report submitted to the U.S. EPA Office of Pesticides in support of a pesticide application, and it is included in the Toxic Substances Control Act (TSCA) docket. The study report includes summary information as well as detailed data from individual animals as described in the appendices to that report. The detailed data were critical to the analyses that were performed in this assessment, allowing the determination of the number of individual animals that were affected by showing adverse responses to both of the critical measures. BMC analysis of this data rendered 77 ppm as the BMCL (95% lower confidence limit of a BMR = 20%).

175. Support for this finding is found in the analysis of the results from activity counts, performed in the same animals (Mandella, 1997). In this measure of neurological effects, the number of times a laser beam is broken was counted during 5-min intervals over the course of the first hour after exposure. A concentration-related reduction in activity counts with increasing concentrations was observed (BMCL = 162 ppm, BMR = 1 SD). Additionally, a supporting study of developmental effects in mice demonstrated that both fetal weight and fetal malformations were discernable from a single exposure (Weller et al., 1999), but these occurred at higher concentration levels (BMCL = 373 ppm, BMR = 0.5 SD) than were seen in either of the two analyses of neurological effects.

176. The MOA for the chosen endpoint for the EtO assessment includes several elements, the first of which is its ready transport into the bloodstream from inhaled air, which allows transport of the parent compound to all parts of the body, including likely penetration of the blood-brain barrier. The evidence presented in Mandella (1997) indicates a rapid clearing of the neurological effects with cessation of exposure, with no lasting irreversible effects at the tested concentrations. The detailed data from the Weller et al. (1999) study on developmental effects from a single exposure also provided data on lethality that could allow a derivation of a value of *n* to be used in the ten Berge (1986) $C^n \times T$ calculation. Previously, a calculation using three studies in rats (a less sensitive species) of two different strains in tests performed in two different labs at only two durations yielded a value of $n = 1.2$. In Weller et al. (1999), the same strain of mice was exposed in the same lab at nearly the same time, for a total of five durations. When analyzed, this resulted in a value of $n = 1.7$.

177. The values derived for each of the acute durations being derived for the Acute RfC for EtO (1-, 4-, 8-, and 24-h) were calculated using a rearrangement of the ten Berge (1986) equation to yield the concentration (C) related to the appropriate duration (T):

$$C^n \times T = k$$

$$C = (k/T)^{1/n}$$

By way of substitution, the concentration values for each of the relevant Acute RfC durations can be calculated as shown below.

$$\text{1-hour value} = (77\ \text{ppm} \times 360\text{-min}/60\text{-min})^{(1/1.7)} = 220\ \text{ppm}$$
$$\text{4-hour value} = (77\ \text{ppm} \times 360\text{-min}/240\text{-min})^{(1/1.7)} = 98\ \text{ppm}$$
$$\text{8-hour value} = (77\ \text{ppm} \times 360\text{-min}/480\text{-min})^{(1/1.7)} = 65\ \text{ppm}$$
$$\text{24-hour value} = (77\ \text{ppm} \times 360\text{-min}/1440\text{-min})^{(1/1.7)} = 14\ \text{ppm}$$

178. Uncertainty factors were applied to the POD following the duration extrapolations used to derive the acute RfC values. A factor of 10 was applied for interindividual variability (UF_H). Because no appreciable differences in blood concentrations of ethylene oxide or ethylene glycol have been demonstrated between mice, rats and humans in physiologically-based pharmacokinetic (PBPK) modeling at exposure levels below 200 ppm, a factor of 3 was applied for interspecies differences (UF_A) for pharmacodynamic differences. The database for ethylene oxide is large and diverse, with acute toxicity, developmental and reproductive toxicity, genetic toxicity (both somatic and germ cells), carcinogenicity, and pharmacokinetics and metabolism information from human and experimental animal studies available, therefore, no additional database uncertainty factor was applied. This yields a composite UF of 30 ($UF_H = 10$; $UF_A = 3$). The resulting acute RfCs for ethylene oxide are presented in Table 3-1.

179. After early consideration as a potential endpoint for the Acute RfC, developmental effects in rats (fetal weight gain decrements and fetal malformations) was determined to be an appropriate endpoint for deriving a Short-term RfC. The three studies used in the derivation of the Short-term RfC values were performed with rats in repeated exposures from gestational days 6-15 (Dow Chemical Co., 1982; Neeper-Bradley and Kubena, 1986; Saillenfait et al., 1996). Observations from epidemiological studies on women of childbearing age occupationally exposed to EtO indicate that developmental and/or reproductive effects also occur in humans (Rowland et al., 1996).

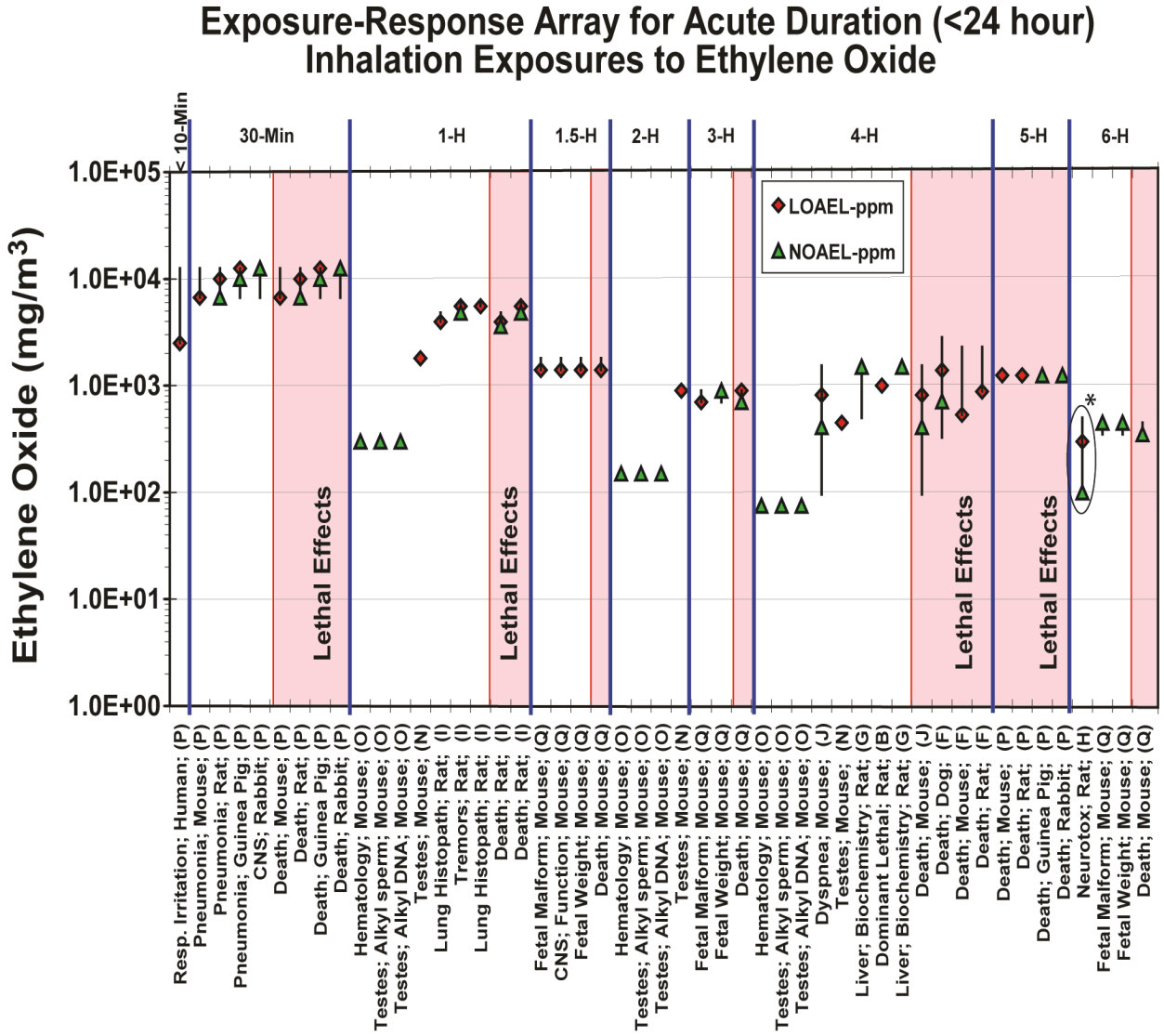

Figure 3-1. Exposure-response array for studies with acute duration exposures to ethylene oxide. *The critical effect (rat neurotoxicity) is circled.

180. As noted in the discussion for the derivation of the Acute RfC, the concentration term seems to be more of a determinant than time at a concentration for ethylene oxide. With these considerations in mind, the duration adjustments applied to generate a 24-h Acute RfC were similarly applied to the 6-h BMCL value to arrive at a 10-day continuous exposure value – application of the $C^n \times T$ equation, with the value of *n* set at 1.7. This results in the 6-h BMCL of 133 mg/m^3 (77 ppm) being adjusted to a 24-h POD of 59 mg/m^3 (34 ppm). An adjustment was also applied to arrive at the 30-day value from the 10-day continuous exposure value, which results in a final POD of 21 mg/m^3 (12 ppm).

181. The same UFs were applied to the Short-term RfC as were used for the Acute RfC – UF_H = 10 and UF_A = 3 for a Total UF = 30. This Total UF was applied to the derived 30-day POD of 21 mg/m^3 (12 ppm) to arrive at a final Short-term RfC value of 0.7 mg/m^3 (0.4 ppm).

182. Figure 3-2 displays a comparison of the Acute and Short-term RfC values for EtO to other reference values. This figure is provided in the appendices in the Toxicological Review for EtO, along with explanatory text to caution the reader that although these values are presented together, they are not interchangeable; occupational values, emergency response values, and screening level values are presented alongside the RfC values strictly for the purposes of showing how these values compare along an exposure and duration continuum. Additionally, it should be noted that the time-weighted average (TWA)

occupational values such as the OSHA PEL or NIOSH REL are designed for repeated work day exposures that may last for a number of years in a worker's career.

183. The database for EtO is fairly large in comparison to many other chemicals; however, to improve this assessment, the greatest need is in defining the relationship of neurological and developmental effects seen in rodents to possible outcomes in humans. The comparison of neurological and developmental effects between species is often difficult to discern.

184. There is high confidence in the values derived in this assessment based on the size of the database and the availability of good supporting data for more than one endpoint (additional neurological measures and developmental effects). The 1-, 4-, and 8-h values are the most reliable, because it is in that duration range (6-h) for which data are available; the lowest confidence is placed on the 24-h value.

3.2 Hexachlorocyclopentadiene (HCCPD)

185. The endpoint chosen for the acute assessment of hexachlorocyclopentadiene (HCCPD) was pulmonary effects in both male and female rats. The study by Ulrich and Hagan (1978) reported significant pulmonary effects that increased in severity with dose. These effects were described as consisting of red focal or diffuse consolidation, progressing to severe generalized hemorrhage and hepatization.

186. The MOA for the chosen endpoint for HCCPD was portal-of-entry effects in the respiratory tract. This has been shown to be the case in both animals and humans and is consistent with the knowledge that HCCPD is a dense, oily liquid from which a corrosive gas can be generated. Tissue damage produced by such a corrosive agent is relatively nonselective, both to the site and to the species exposed.

187. Dose/exposure response analysis for HCCPD was based on the study by Ulrich and Hagan (1978). The NOAEL approach was used because of the lack of quantitative data for dose-response modeling of nonlethal effects.

188. Duration extrapolation was performed using the ten Berge modification of $C^n \times T$. A slope value *n*, as described in ten Berge et al. (1986), was derived for HCCPD using lethality data from Treon et al. (1955). The duration extrapolation for HCCPD was based on mortality instead of on pulmonary portal-of-entry effects, because the mechanism for the two processes is believed to be the same. This is supported by the qualitative description of lung injury found at necropsy and described in clinical findings, in both the animals that died from exposure to higher concentrations and in those that survived exposure to lower concentrations (Treon et al., 1955; Ulrich and Hagan, 1978). The pulmonary pathology noted in both studies suggests that the pulmonary damage observed following acute exposure is part of the pathway leading to mortality. This association provides a basis for using the relationship between mortality and exposure duration for extrapolation of data for the less severe endpoint.

189. The database for acute inhalation toxicity of HCCPD consists mostly of lethality information with qualitative descriptions of pulmonary injury. The database lacks reproductive/developmental studies in animals following inhalation exposure to HCCPD.

190. There is medium confidence in the RfC values derived in this assessment based upon the limited database of information that exists and the availability of data from several exposure durations (1-, 3.5-, and 7-h) that allowed the generation of an endpoint-specific value of *n* for use in the duration extrapolation. The 1-, 4-, and 8-h values are reported in Table 3-2 of this assessment and are reliable, based on the exposure duration data that is available. The 24-h value was not derived because of a lack of data to support this extrapolation. It should also be noted that the 8-h Acute RfC for HCCPD is only a factor of 10 greater than the Chronic RfC.

Table 3-1. Acute RfC Values for Ethylene Oxide

	Hours			
	1	**4**	**8**	**24**
Derived Values (ppm)	220	98	65	34
Units Conversion (mg/m^3)	398	176	117	61
HEC Conversion Factor	1	1	1	1
HEC (mg/m^3)	398	176	117	61
Total Uncertainty Factor	30	30	30	30
Acute RfC (mg/m^3)	13	5.9	3.9	2.0

3.3 Hydrogen Sulfide (H_2S)

191. As shown in Figure 3-3, the available studies indicate that the respiratory tract is a primary target organ system of hydrogen sulfide (H_2S) toxicity. Respiratory tract endpoints examined ranged from clinical signs to biochemical (e.g., cytochrome oxidase inhibition) and pathological changes in respiratory tract tissue. Among systemic endpoints, metabolic and cardiac effects were also noted. Taken together, the results from the majority of these studies suggest that H_2S-induced inhibition of aerobic metabolism may be a common MOA underlying the endpoints investigated.

192. Categorical regression was chosen for both the exposure response and duration analysis of H_2S because of the multiple studies available. For inhalation scenarios, categorical regression uses response data (classified by severity category) and the associated exposure data (concentration and duration) to estimate the probability, or likelihood, that an effect of a certain severity will occur at various concentrations and durations of an inhaled chemical.

193. For comparative purposes, a BMC analysis was also performed on the nasal lesion incidence data from the Brenneman et al. (2002) study. Unlike the categorical regression approach, which provides reference values of various severity effects for differing durations, the BMC approach provides a reference value based on actual (vice severity-transformed) dose-response data (either incidence or continuous) but only for that duration (in this case, 3 h) of the study used to derive the POD

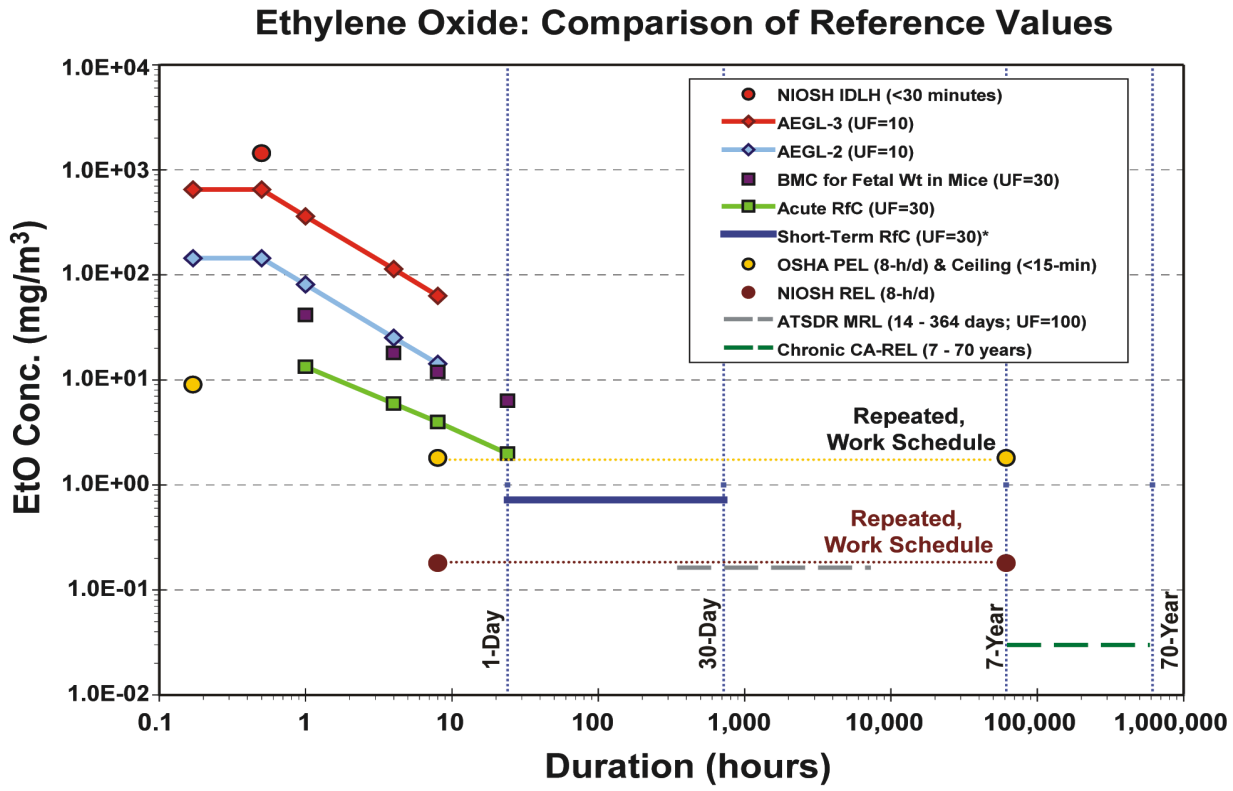

Figure 3-2. Comparison of the Acute and Short-term RfC values for ethylene oxide with other existing reference values.

Table 3-2. Proposed Acute RfCs for HCCPD

Exposure Duration	Acute RfC
1 hour	0.007 mg/m^3
4 hours	0.003 mg/m^3
8 hours	0.002 mg/m^3
24 hours	(not supported)
Chronic RfC	0.0002 mg/m^3

194. Data from 6 human and 14 animal studies were used for the quantitative analysis. Categorical regression analysis provided information on species sensitivity and also provided concentration-duration relationships to calculate the points-of-departure (the one-sided 95% lower confidence limit for mild adverse effects) for differing time points (1, 4, 8, and 24 h). A total UF of 10 to account for within-species variation was applied to each of these values to derive the acute RfC values presented in Table 3-3. The application of additional UFs was not warranted because of the number of studies used in the analysis, the use of model analysis to calculate points-of departure, and the use of human data (as the most sensitive species) in the model analysis.

195. The acute toxicity data set for H_2S is quite robust. Data from 21 references (6 human and 15 animal studies) with adequate information on number of subjects, exposure concentration, duration, and response were available for analysis. Overall, the database could be improved by the addition of studies that would provide further MOA information examining the role between impaired aerobic metabolism (inhibition of cytochrome oxidase) and H_2S-induced effects.

196. The overall confidence in the values derived in the H_2S assessment is high. Confidence in the database is high because numerous studies in several species were used in the quantitative analysis and because the database includes studies for relatively mild effects in humans. Collectively these studies provide useful dose-response characterization sufficient for evaluation not only of the dose-response relationship but also of the duration-response relationships. In addition, the Acute RfC values derived form the categorical regression analysis were found to be concordant with both the AEGL-1 interim values for similar durations, and the 3-h value calculated from the BMC analysis of the Brenneman et al. (2002) study as shown in Figure 3-4.

197. Thus, there is a degree of consistency among values derived from different analyses. Consequently, confidence that the Acute Reference Concentrations protect against mild adverse e ffects in humans is high. The value for the Chronic RfC is also shown in Figure 3-4 for comparative purposes.

3.4 Phosgene

198. The exposure-response array shown in Figure 3-5 displays the low and high exposure concentration used in the individual studies, and if identified, the BMCL, NOAEL, and LOAEL (y-axis) identified from the respective study categorized by endpoint and species (x-axis). The x array illustrates the extensive information available on the adverse effects of phosgene on the respiratory tract, affirming the respiratory tract as a major target organ of inhaled phosgene across species. Immunotoxicological effects are also presented within the array. Concentration-duration relationships resulting in lethality are shown for comparative purposes.

199. The endpoint chosen for the acute assessment of phosgene was respiratory effects in rodents. The pathologic progression of effects and toxicological events documented in the lower respiratory tract that follow from acute lethal exposures to phosgene (i.e., through various stages and degrees of pulmonary edema) appears to be parallel across species. Net deficiencies in respiratory tract immunological response has also been noted following phosgene exposures to similar concentration levels in both rats and mice. However, a lack of information on the MOA for these immunotoxic effects engenders considerable uncertainty in areas critical to dose-response assessment.

200. The MOA for the chosen endpoint for phosgene is thought to involve the acylating properties of this chemical, although HCl production may play a minor role (U.S. EPA, 1986). At the subcellular level, biochemical mechanisms may include alterations in various respiratory tract enzyme systems (e.g., cytochrome oxidase, ATPase, and LDH) or changes in mitochondrial oxygen uptake or respiratory activity that compromise cellular integrity. The underlying MOA of phosgene's immunotoxicology is less known than, and probably unrelated to, its edematogenic effects.

201. The dose/exposure response analysis for phosgene was based on a categorical regression of all respiratory effects observed in either rats, mice, or guinea pigs using CatReg software. NOAEL/LOAEL and BMD analyses were also performed, and they substantially support the CatReg analysis.

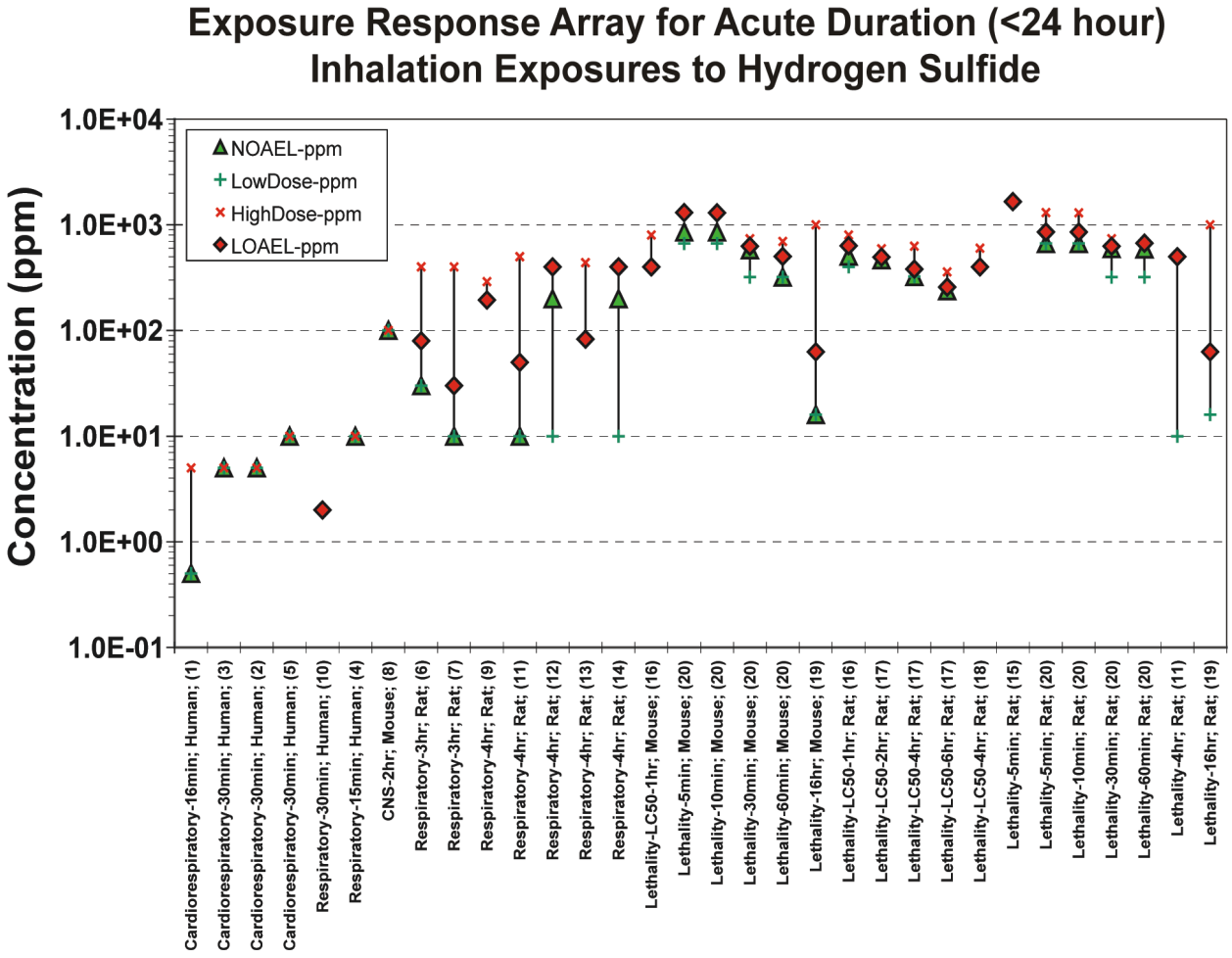

Figure 3-3. Exposure-response array for studies with acute duration exposures to hydrogen sulfide.

Table 3-3. Derivation of Acute RfC Values for Hydrogen Sulfide from Categorical Regression Results

Exposure Duration (hours)	Human EC-T10 (mg/m^3)	95% LCL (mg/m^3)	UF	Acute RfC (mg/m^3)
1	5.02	2.99	10	0.3
4	3.01	1.75	10	0.2
8	2.33	1.33	10	0.1
24	1.55	0.85	10	0.09

202. Duration extrapolation was based on the CatReg analysis of respiratory tract effects in rats, mice, and guinea pigs. The results indicate that for up to 8-h of exposure, respiratory tract effects seem to follow Haber's relationship (effects vary with $C^n \times T$, $n = 1$). Only two time points for mice were available (4- and 8-h), but the data for a respiratory immunotoxicity endpoint (death following bacterial infection) from phosgene exposure to mice follow a similar C × T relationship.

203. In general, UFs are applied to the point of departure to account for uncertainties in extrapolation from LOAEL to NOAEL, extrapolation from rodent bioassay data to human exposure conditions, for unknown variability in human sensitivities, and for data deficiencies. Current EPA practice includes use of partial UF such as 101/2 under conditions where toxicokinetics and mechanistic information are available (U.S. EPA 1994) and/or data are available on the nature and extent of variability in human susceptibility. The default UF for interspecies extrapolation and within-species variability are each 10. Half of that factor, 101/2 , or 3, reflects the pharmacokinetic component of uncertainty and half represents the pharmacodynamic component of uncertainty. The use of a dosimetric adjustment factor accounts for the pharmacokinetic component of interspecies uncertainty and justifies the use of 101/2 or 3 to account for the pharmacodynamic component of interspecies uncertainty. Since there are no data documenting the nature and extent of variability in human susceptibility for phosgene, the default UF of 10 is used for within-species variation. Thus, a total UF of 30 (3 for pharmacodynamic differences × 10 for intraspecies variability) was applied to the PODs to derive acute RfCs for 1, 4 and 8 h (Table 3-4).

204. Figure 3-6 shows the comparisons between reference values for phosgene. It should be noted that an AEGL-1 value for phosgene could not be developed. Comparison of the AEGL-2 values to the Acute RfC values for phosgene at 1, 4, and 8 h shows that these values differ by just over three orders of magnitude. The Acute RfC values are lower, which is consistent with their intention to represent a safe exposure level that is not likely to cause adverse effects in a human population, including sensitive subgroups, whereas exposure of these same human populations to an AEGL-2 may result in irreversible, long-lasting effects or effects which impair the ability to escape. The IRIS chronic inhalation RfC (3×10^{-4} mg/m^3) is lower than the Acute RfC at 8 h by approximately only a factor of 20, which is consistent with phosgene's acute toxicity and the fact that immunological and respiratory effects associated with very low level acute exposures do not appear to progress or regress significantly following extended or repeat exposures.

205. The database for acute inhalation toxicity of phosgene is extensive, but consists mostly of studies describing effects associated with lethal exposures. Information on immunotoxic effects of sublethal exposures exist from studies of rats and mice, but little is known about the MOA for these effects. This engenders considerable uncertainty in areas critical to dose-response assessment, such as relevancy to humans (including potential susceptible populations and lifestages), and in the character of dose-response at relevant concentrations and durations. Studies that would help elucidate these areas of uncertainty would be helpful.

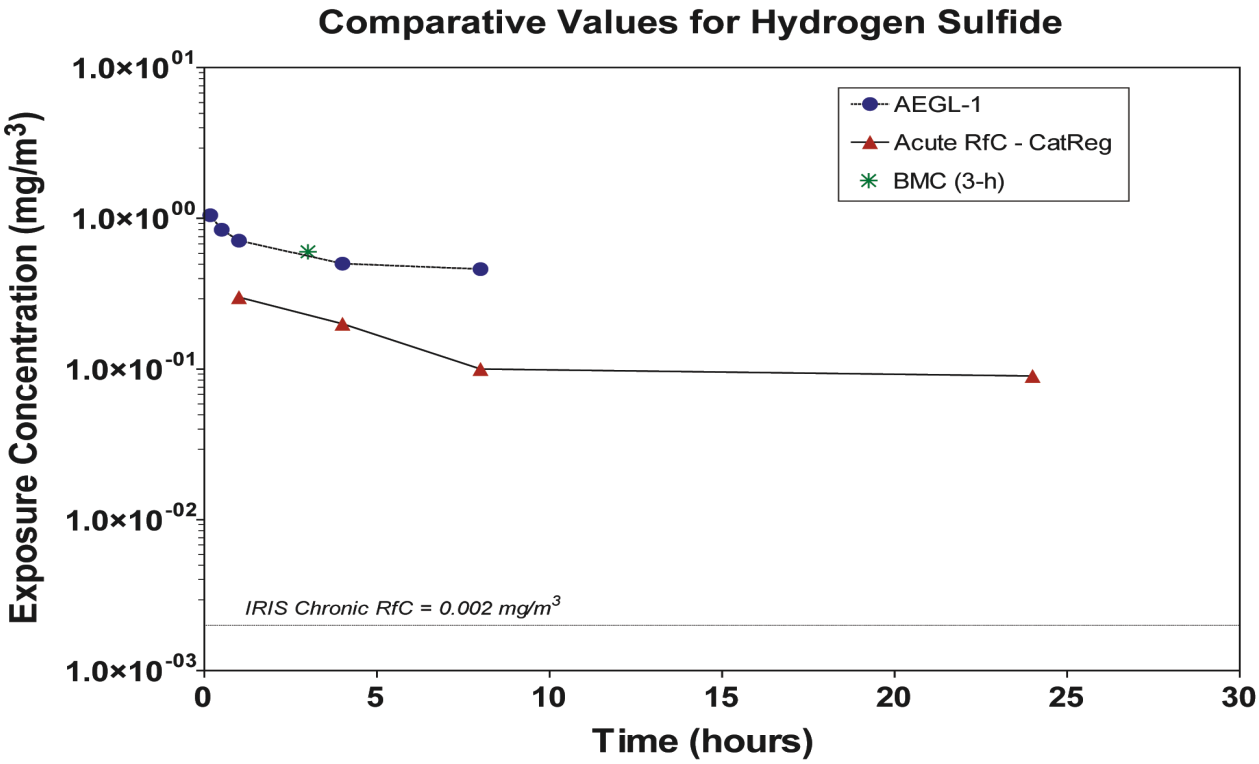

Figure 3-4. Comparison of Acute RfC for hydrogen sulfide with other existing reference values, and to the BMC results from analysis of the Brenneman et al. (2002) study.

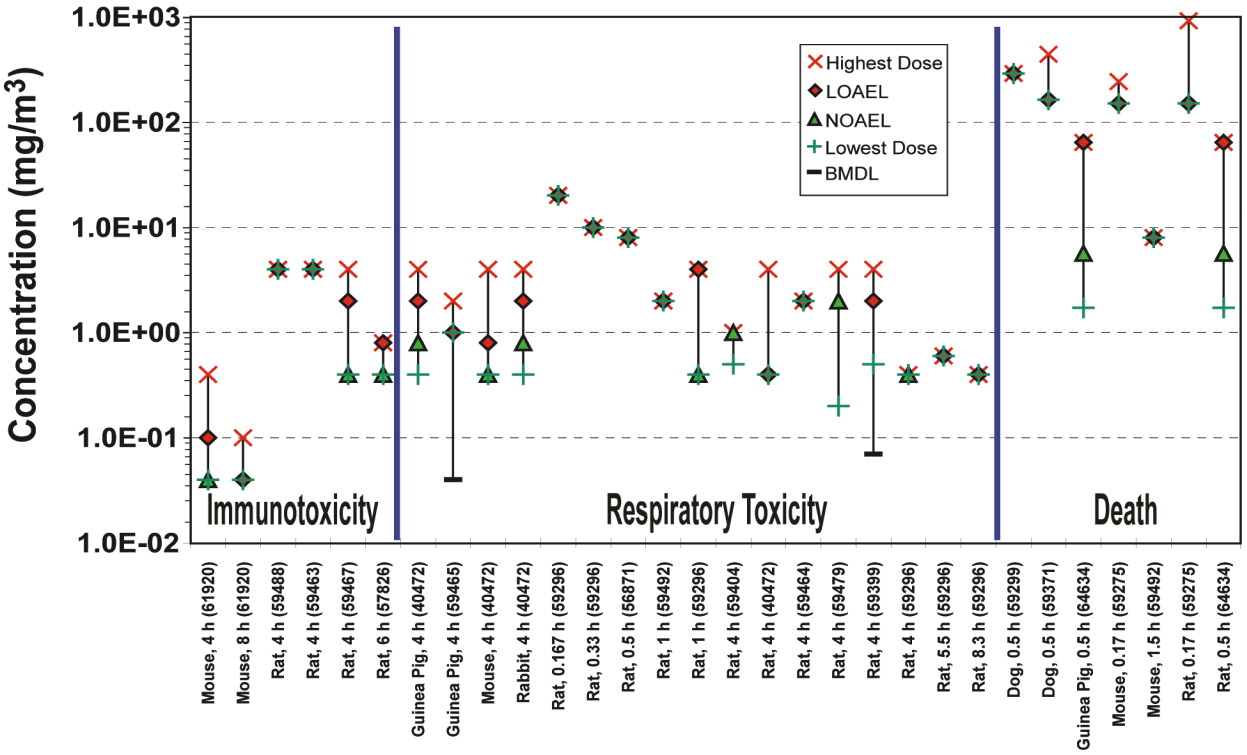

Figure 3-5. Exposure-response array for studies with acute duration exposures to phosgene.

Table 3-4. Comparison of Derived Acute RfC Values for Phosgene With AEGL Values and With the Proposed Chronic RfC

Exposure Duration	AEGL-3 (mg/m^3)	AEGL-2 (mg/m^3)	AEGL-1 (mg/m^3)	Acute RfC (mg/m^3)
10 minutes	14.4	2.4	NR	—
30 minutes	6.0	2.4	NR	—
60 minutes	3.0	1.2	NR	0.005
4 hours	0.8	0.32	NR	0.001
8 hours	0.36	0.16	NR	0.0007
Proposed 2005 Draft Chronic RfC (mg/m^3), U.S. EPA, IRIS				$3 \times 10{-}4$ (0.0003)

206. The otherwise extensive nature of the database and the fact that observations and measured responses are both qualitatively consistent across a variety of species and experimental designs and quantitatively consistent across three different approaches (NOAEL, LOAEL, BMD, and CatReg) allows this assessment to be evaluated as having a medium to high confidence level. Data that could address key areas of uncertainty would be information relating to pharmacodynamics for such a direct-acting agent that would allow cross-species examination of the similarity or divergence in portal-of-entry tissues under conditions of identical target-tissue doses. Resolution of matters and issues regarding the qualitative and quantitative evaluation of immunotoxic endpoints (e.g., BMD analysis procedures) would also reduce the uncertainty inherent in the assessment of the toxicity of this agent.

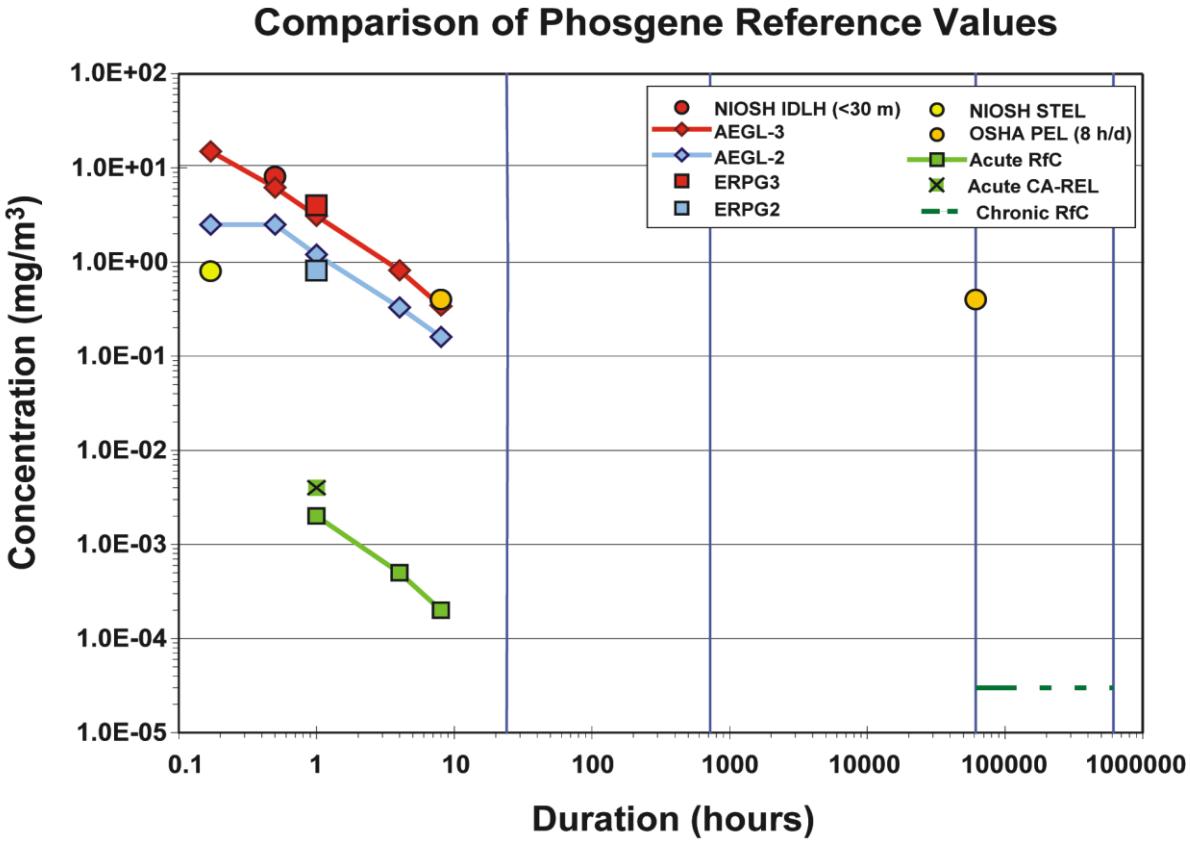

Figure 3-6. Comparison of the Acute RfC for phosgene with other existing reference values

4. SUMMARY AND PROJECTIONS TO COMPLETE THE ACUTE INHALATION METHOD

207. This section of the Preliminary Methodology Document seeks to provide an overview of what has been gained (i.e., lessons learned) from the development of the four example Acute RfC assessments and to project what will be necessary to bring the acute inhalation risk assessment method to completion. This includes a discussion of the types of effects that have been addressed in these assessments in comparison to the many effects that are reasonably expected to be encountered from acute exposure scenarios with various chemical agents.

208. A summary of many of the potential endpoints that might be considered in acute assessments is presented in Table 4-1, along with the concentration-response and duration approaches that are available for such an analysis. Table 4-1 includes those endpoints for which test guidelines have been developed and other endpoints the U.S. EPA typically considers in assessment activities, and although thorough, it should not be seen as exhaustive.

209. The principal focus of Table 4-1, however, is the role of the four sample assessments in this document in demonstrating the use of procedures and approaches described in Chapter 2 and the manner in which the various endpoints are identified, analyzed, and evaluated within the context of an acute scenario.

210. The intent of Table 4-1 is to provide a pointer to potentially useful examples for an investigator intending to cover similar aspects for a different chemical. This summary may also help guide decisions on which additional chemicals might be included in additional rounds of developing acute inhalation example assessments, as will be discussed further.

4.1 Lessons Learned

211. Much has been covered in the development of the example assessments. As shown in Table 4-1, however, there are still many types of endpoints that have yet to be addressed and it is expected that additional lessons will be learned with each new assessment.

212. Another goal of this final summary section is to review what has been gained from this first set of example assessments in order to inform how to proceed with the task of developing an inhalation assessment method for acute and other less than lifetime durations.

4.1.1 Endpoint-Specific Lessons

213. Respiratory effects (portal-of-entry effects) were a major consideration for three of the four example assessments and were used as the POD for derivation of the Acute RfC in all three cases. Portal-of-entry effects are often the concern for acute exposure scenarios, and they are often manifested shortly after the exposure event.

214. Although neurological effects were chosen as the critical effect for acute exposures to EtO, the consideration of the potential for developmental effects from a single exposure posed a number of challenges. These challenges included constructing a rationale for use of an endpoint in which protocols typically involve multiple-day repeated exposures. As noted in Chapter 2, most developmental studies employ repeated exposures over the course of a number of days, which may or may not be applicable to a single exposure scenario; therefore, MOAs for the developmental effects need to be considered before use in an acute assessment. In the case of EtO, there is both an MOA argument (EtO is a DNA-reactive chemical) and empirical evidence (the study of Weller et al., 1999, which demonstrated developmental effects from a single exposure) to support the use of a developmental endpoint in an acute setting. However, when the detailed data from the Weller et al. (1999) study was analyzed using a BMC approach, the resulting BMCL values (373 ppm at 3 h) were over 3-fold higher than the NOAEL for neurological effects (100 ppm at 6 h). Although this analysis resulted in developmental effects not being adopted in the acute assessment for EtO, it served to demonstrate that this type of effect may be used for an acute assessment. Additionally, the previously published analyses using BMC analysis of developmental effects were used to establish the appropriate parameters (e.g., BMR) for similar analyses. The analysis of developmental endpoints resulted in the derivation of a Short-term RfC value for EtO.

Table 4-1. Summary of Endpoints and Analytical Options Covered by the Example Acute Assessments

	Example Acute Assessment			
Target Organ/System Endpoint	**Ethylene Oxide**	**HCCPD**	**Hydrogen Sulfide**	**Phosgene**
Respiratory		▲▲	▲▲	▲▲▲
Cardiovascular			▲	▲
Hematological				
Musculoskeletal				
Skin				
Eyes				
Gastrointestinal				
Renal-urinary				
Hepatic				
Immunological				▲
Reproductive	▲			
Developmental	▲			
Neurological	▲▲		♦	
Endocrine				
Metabolic poison			♦	♦
Genetic	▲			
Lethality			♦	♦
Concentration-Response Approach				
NOAEL	▲	▲▲	▲	▲
BMC	▲▲		▲	▲
Categorical regression			▲▲	▲▲
Meta-analysis	▲▲			
Duration Approach				
Default*				
Based on lethality slope	▲▲	▲▲		
Endpoint-specific	▲			
Categorical regression			▲▲	▲▲

▲ This Endpoint/Option was also investigated and reported upon.
▲▲ The Critical Endpoint or Chosen Option for the subject assessment.
♦ Endpoints used in the Categorical Regression analysis.
* The default value of $n = 3$ for extrapolations to shorter durations and $n = 1$ for longer durations than the Observed data points.

215. The Acute RfC for HCCPD was based on frank effects on the tissues of the lung. The data set for HCCPD was limited, and therefore, consideration of effects on other endpoints was not possible.

216. H_2S has effects on the upper respiratory tract (nasal tissues) at low concentrations, on lung tissues at higher concentrations, and on the CNS at yet higher concentrations. Based on the available information suggesting that inhibition of cytochrome oxidase is likely to be the common MOA underlying effects seen at low concentration, including cardiorespiratory, cardiac, and metabolic effects, all were included in the CatReg analysis for this chemical.

217. In the case of phosgene, quick-acting effects on lung tissues made this agent a potent chemical warfare agent. A strength of this acute assessment on phosgene is construction of an ordered evaluation of the extensive information available on the progression of the pulmonary pathology. Immunological effects within the lungs have also been noted for phosgene, although the data set for this endpoint is not robust and the understanding of the MOA for immunological effects is not well characterized. The lessons learned from the assessment of the acute effects for phosgene included highlighting the lack of understanding of acute chemical exposures on the immune system. Effects from acute inhalation exposure to phosgene as well as dermal exposures to EtO have shown that an acute exposure can result in an immunological effect.

4.1.2 Concentration-Response Approaches

218. The analysis of EtO was centered on the use of the BMC approach to determine the POD for both an acute and short-term assessment. Additionally, a meta-analytical approach was used in a deriving the POD for the Short-term RfC.

219. HCCPD demonstrated how a sparse data set, if it contains the proper information, can be used in the derivation of an Acute RfC. This assessment was limited to the use of the NOAEL approach because of those data limitations.

220. H_2S was an example of the use of categorical regression in development of an Acute RfC using multiple related endpoints with varying severity to inform the analysis. Comparison of the results from the categorical regression analysis to an assessment of both the BMC and NOAEL approaches was also performed, lending support to the POD determination with CatReg and highlighting the benefits of performing as many exposure-response analytical approaches as possible.

221. Phosgene was another example of the use of categorical regression, but in this instance, using the analysis of a single endpoint across species to help inform the derivation of a final POD value. As with H_2S, the application of another approach (i.e., BMC) to this data set helped support the final POD derivation.

4.1.3 Duration Approach

222. None of the example assessments used the default duration approach, as described in Section 2.6.3.

223. Both EtO and HCCPD utilized a duration slope factor that was derived from available lethality data. Calculation was by the method described by ten Berge et al. (1986).

224. Both phosgene and H_2S used the categorical regression approach wherein both a duration- and exposure-response analysis were provided. For H_2S, PODs for 1, 4, and 8 h were determined directly from the concentration-duration slope generated by the CatReg analysis. In the case of phosgene, however, the application of the duration slope factor derived from the categorical regression analysis was applied to the results from the BMC and NOAEL approaches for duration extrapolation, (i.e., the slope of the concentration-duration curve was made to intercept the POD concentration and duration obtained from BMC analysis). PODs for 1, 4, and 8 h were then obtained from this line and intercept.

4.2 Next Steps

225. The goal of this section of this document is to outline ongoing efforts to develop background information and supporting methods (i.e., tools) useful in progressing to a final acute inhalation assessment

method. Part of the anticipated effort will be the development of additional example assessments to address some of the endpoints that have not been investigated for acute effects with this method; these will undoubtedly uncover issues that have not been considered as yet. Finally, some discussion is provided to outline the process leading to development of a final method document. A compilation of less-than-lifetime inhalation assessment methods will also be developed in the future.

4.2.1 Development of Additional Tools and Supporting Background Information

226. There are a number of ongoing activities that will help support development of additional acute assessments and an acute inhalation method and, in many cases, also provide support for assessments for other durations.

- **Dosimetry Analysis Project.** This project seeks to elucidate some duration-specific dosimetry issues. For example, the assumption in developing chronic inhalation reference values (i.e., the Chronic RfC) is that there is a steady-state relationship between the ambient concentration in air and the internal dose. This is not the case. The relationship is very chemical-specific when looking at an acute exposure scenario, where it may take hours to reach a steady-state, and a value for a 1-h exposure duration is needed.
- **Database of Exposure-Response Values.** In this project, the data used to develop the Acute RfC values will be documented and stored for future use. The goal of this project will be to serve as a repository for the raw study data used in the exposure-response analyses leading to the derivation of the Acute RfC. This resource will also be amenable to use with data from other durations (e.g., throughout the IRIS program).
- **Comparisons of Acute Reference Values in Support of Developing an Acute Assessment Method.** This is a joint project with the Office of Air Quality Planning and Standards of the Office of Air and Radiation. The dual role for this analysis is to help inform the process of developing the acute inhalation assessment method and to provide support for the analysis of residual risks for hazardous air pollutants, as mandated in the 1990 CAAA.
- **Updates and Revisions to the Categorical Regression Software.** The current version of the CatReg program is written to operate using proprietary software only. In this revision, the program will be converted to operate using the open-source "R" platform. Additionally, fixes to identified problems in the program code and improvements to analytical utility will be made, and revised versions of both the User's Guide and the Technical Guide will be developed.
- **Updates and Revisions to the Benchmark Dose Software.** Improvements to and additions of the models available in the software continue to be made. Future versions will facilitate the analysis of dose-response data for different exposure durations and endpoints by automating the BMDS modeling and reporting features to include batch processing and summary tables of comparative results.

4.2.2 Additional Example Assessments

227. As noted in Table 4-1, there are many endpoints that were not covered in this initial set of four assessments. It is anticipated that as the work leading to a final acute inhalation assessment method progresses, application of the developing method to additional chemicals will provide new insights on issues yet to be considered. For example, the assessment for EtO provided an example for performing an acute assessment using developmental effects.

228. In addition, each data set analyzed will present its own challenges and opportunities. In the case of HCCPD, the challenge was to work with an extremely limited data set. Sometimes even more daunting is the challenge of working with a wealth of data, as was the case for EtO, H_2S, and phosgene. The opportunity to develop a meta-analytical approach, as illustrated in the EtO example, was based on the available data set and was mostly independent of the endpoint under consideration. Therefore, the size and nature of the data set as well as the endpoint should be a consideration in choosing chemicals for additional example assessments.

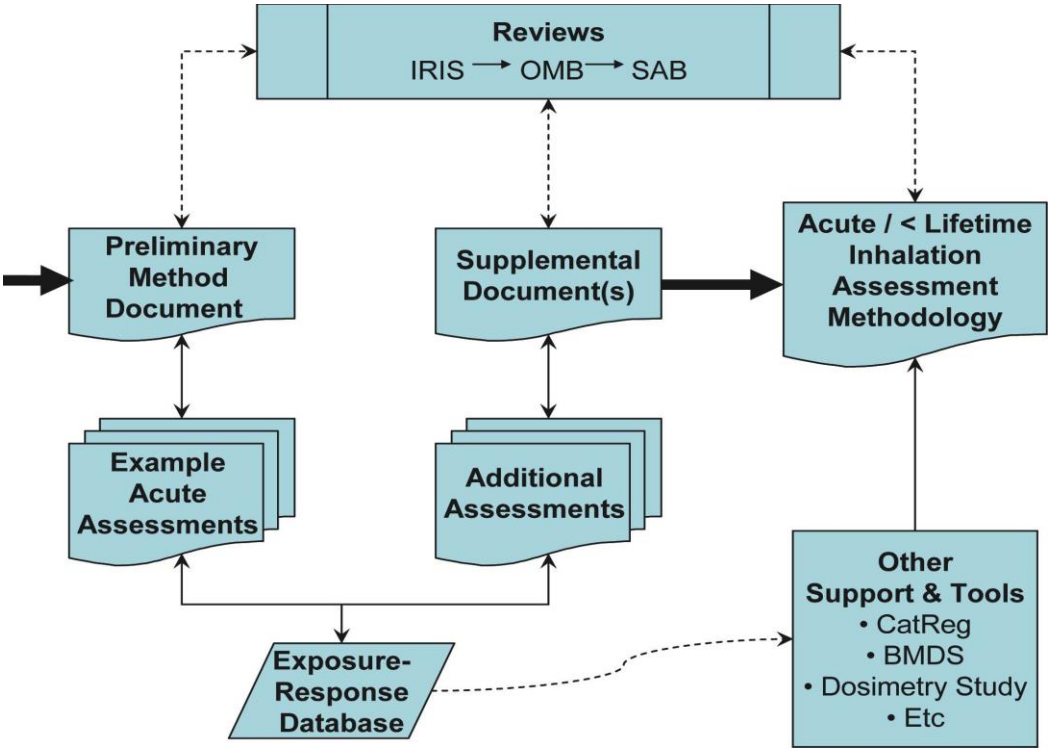

Figure 4-1. Anticipated process for completion of an inhalation assessment methodology for acute and other less than lifetime durations.

4.2.3 Process to Develop an Acute Inhalation Methodology

229. Figure 4-1 provides the steps and pathways anticipated in progressing to a Final Methodology. This Preliminary Methodology Document is the first in a series of steps included in this process and has been preceded by substantial efforts not included in this diagram, most notably the Draft ARE (U.S. EPA, 2000a) and the comments from that document from the SAB and RAF. The review of this document (along with the four example assessments) is anticipated to follow the same review process as provided through the IRIS program, followed by an interagency review lead by the Office of Management and Budget (OMB), and finally, an SAB review.

230. The Exposure Response Database noted in Figure 4-1 is a continuation of the database previously developed to assist in this method development process (Guth and Raymond, 1996), and is being updated and expanded for greater utility in performing exposure response assessments across all durations. Similarly, existing analytical tools available for performing 1 exposure response assessments (e.g., CatReg, BMDS) are being updated and improved, as discussed in Section 4.2.1.

231. Additional assessments are anticipated to occur to help inform the method development process on endpoints and other issues not covered in the set of four example assessments, as discussed in Section 4.2.2. As those issues are identified and resolved, additions or supplements to this document are anticipated. These supplemental documents would also receive reviews, perhaps as rigorous as those anticipated for this document.

232. Two basic, distinct approaches are used in the assessment of health effects by the U.S. EPA: stochastic and deterministic. In the case of a stochastic approach, exposure is considered to lead to risk that accumulates over time even after exposure ceases (e.g., cancer risk from exposure to a mutagenic carcinogen). In the case of a deterministic approach, risk is considered to be limited to the length of the actual exposure (e.g., noncancer risk from exposure to a solvent). This contrast leads to fundamental differences in the relationship of duration and risk for cancer and noncancer approaches. In the case of

stochastic approaches, risk from an exposure can be reasonably apportioned over time, whereas for deterministic processes, risk is limited and can be assessed only during the period the agent is present. Thus, assessment of risk from deterministic noncancer effects can only be assessed at the durations of interest. It is recognized that durations of interest exist for the risk assessment community other than acute and chronic. It is, therefore, likely that subsequent supplemental documents indicated in Figure 4-1 will deal with durations intermediate between acute and lifetime (i.e., less than lifetime). Thus, the final methodology document is anticipated to address less-than-lifetime durations, including acute durations.

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